Ingemar Cullhed

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ALMQVIST & WIKSELL

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AORTIC STENOSIS

A clinical study of aortic stenosis, isolated or combined with aortic insufficiency, with special reference to haemodynamic and angiocardiographic observations

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AORTIC STENOSIS

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To
Inger
and
Marie, Susanne and Thomas

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ABBREVIATIONS

AI	Aortic insufficiency
AS	Aortic stenosis
ASAI	Aortic stenosis with aortic insufficiency
AVD	Arteriovenous oxygen difference in ml/l
BTPS	Body temperature, ambient pressure, saturated
CI	Cardiac index in $l/min \cdot m^2$
CO	Cardiac output in l/min
HR	Heart rate
Kpm	Kilopondmeter (100 kpm/min = 723 footpounds/min = 16.35 W)
LV	Left ventricle
LV_{ED}	Left ventricular end-diastolic (pressure)
LVH	Left ventricular hypertrophy
PA	Mean pulmonary artery (pressure)
PAW	Mean pulmonary artery wedge (pressure)
PSG	Peak systolic pressure gradient in mm Hg
RA	Mean right atrial (pressure)
STPD	Standard temperature and pressure, dry
SV	Stroke volume in ml
$\dot{V}_{O_2}$	Oxygen uptake in ml/min
I–IV	Functional classification (see page 11)

Statistical symbols (see appendix 1)

M	Mean
S.D.	Standard deviation
S.E.	Standard error of the mean
*, **, ***	Significance asterisks

Chapter 1

INTRODUCTION

Although attempts were made more than 50 years ago (Tuffier 1913), it was not until 1950 that Bailey performed the first successful operations for aortic stenosis. Essential improvements resulted from the introduction of extra-corporeal circulation, which is a prerequisite for radical operations involving reconstruction and replacement of the aortic valve which are now performed in many places, including this hospital.

Clinical diagnosis of aortic stenosis has been possible since the beginning of the 19th century. The rapid development of cardiac surgery necessitated more reliable pre-operative diagnosis, both qualitatively and quantitatively. This was made possible by the development of methods for catheterization of the left heart, for pressure measurement and contrast injection.

In this hospital surgical treatment of aortic stenosis has been performed since 1958. During the five-year period 1958–1962 sixty-seven patients with aortic stenosis have been referred here for examination and decision as regards operation.

The aim of this investigation was to study this five-year material from different aspects. The first part deals with studies of the haemodynamics at rest and during exercise, with special consideration of factors influencing the magnitude of the peak systolic gradient. The occurrence of subjective symptoms, physical signs, and changes in the electrocardiogram and chest radiogram in relation to the objective degree of severity as manifested by the pressure gradient is also studied. In the second part the angiographic diagnosis of aortic stenosis and aortic insufficiency is discussed, and a comparison made between the degree of severity as assessed angiographically and haemodynamically. An essential question studied was that of the reliability of different clinical and angiographical signs of aortic stenosis in relation to the pressure gradient measured.

Chapter 2

CASE MATERIAL

During the period 1958–1962, 397 adult patients with aortic and mitral valvular disease were examined. Of these cases 57 % had isolated mitral valvular disease, 25 % (99 cases) isolated aortic valvular disease and 18 % both conditions combined. Added to the 99 adult cases with aortic valvular disease, there were 9 cases who had been investigated at the pediatric clinic. Of this total of 108 cases, 43 had stenosis (group AS, cases 1–43), 24 combined stenosis and insufficiency (group ASAI, cases 101–124) and 41 cases aortic insufficiency (cases 201–241). This study deals with the 67 cases with stenosis (groups AS and ASAI). Since only 26 of these 67 cases came from the hospital's own receiving area the material is selective. The frequency of isolated aortic diseases in clinical materials of so-called rheumatic heart disease has been given as 15 %–22 % (White 1937, Hall 1961).

Cases with subvalvular stenosis were excluded, as also were those with other congenital heart disorders. In one case a mild degree of mitral stenosis was found (case 120, appendix 2), and in some cases mild mitral insufficiency was found on left ventricular angiography. In one patient (case 33, appendix 2) the case history and clinical signs indicated previous non-rheumatic myocarditis. Among other diseases found were hypercholesterolaemia in 2 cases (see below) and Laennec's cirrhosis in one case.

Pressure measurements in the left ventricle were performed in all cases, and also, with one exception, angiocardiography or aortography. Two cases had been examined at Karolinska Sjukhuset and Södersjukhuset, Stockholm, respectively, and two cases had been operated on at Karolinska Sjukhuset.[1] Autopsy had been performed on 26 cases. 28 cases were operated on with the open technique and 5 with the closed technique.

Classification

From a *diagnostic* aspect the material was divided into the two groups AS and ASAI. This classification was based on the author's evaluation of the compiled results of the clinical, haemodynamic and roentgenological investigations, and also in some cases of the findings at operation or autopsy. The patients assigned to group AS were all those with signs of aortic stenosis and in whom aortic insufficiency appeared to be either completely absent or mild (at the most grade 2 according to aortography, cf. chapter 5). Group ASAI comprised cases with signs of aortic stenosis and with aortic insufficiency of grade 3 or 4 according to aortography.

The differentiation from diseases of other

[1] I would like to thank Professor Clarence Crafoord and Associate Professors Bengt Jonsson, Björn Nordenström and Håkan Arvidsson for generously placing at my disposal operation reports, haemodynamic data and angiographic films on these cases.

TABLE 1. *Distribution of the cases with respect to the functional and the objective classification.*

Funct. classif.	AS				ASAI				
	PSG				PSG				
					0–49		50–152		
	0–24	25–74	75–133	Total	AI:3	AI:4	AI:3	AI:4	Total
I a	5	4	1	10	—	2	—	—	2
I b	5	4	3	12	2	1	1	—	4
II	2	8	4	14	1	—	3	7	11
III+IV	—	1	6	7	—	3	2	2	7
Total	12	17	14	43	3	6	6	9	24

AI:3, AI:4, see page 95.

valves appears to be distinct. The most reliable method for classification into AS and ASAI is thoracic aortography, which was performed on all patients with ASAI but on only half of those with AS. As will be discussed later (chapter 6) there seems to be a correlation between the intensity of the diastolic murmur and the degree of AI. It was therefore considered permissible to classify patients into the two groups even when a diastolic murmur was present and aortography had not been performed. There remains, however, some uncertainty for borderline cases—regarding degree of AI between groups AS and ASAI, as well as degree of AS between groups ASAI and AI.

The *functional classification,* into classes I–IV, was made according to the New York Heart Association (1964). Since there were but few cases who were greatly disabled, groups III and IV were combined. In some connections class I was sub-divided into I a: symptom-free, and I b: with symptoms.

Different modifications of functional classification have been suggested for aortic stenosis, both on the sole basis of certain subjective symptoms (e.g. Glover & Gadboys 1958, Baker & Somerville 1959, Hancock & Fleming 1960, Baird & Bigelow 1960) and in consideration of objective changes also (Gorlin, McMillan, Medd, Matthews & Daley 1955, Kremer 1960). In order to facilitate comparisons with other series and other heart disorders the purely functional classification has been used here.

Classification into *degrees of objective severity* was made according to the peak systolic gradient (PSG) and, for ASAI, also according to the degree of aortic insufficiency, as discussed in chapters 3 and 5. The classification of the patients according to the degree of disability and the degree of objective severity is shown in Table 1. It is seen that some isolated cases in class I had pronounced AS or ASAI, whereas no cases in class III+IV had mild AS or ASAI.

Age and sex

The distribution according to *age* may be seen in Table 2. There were more cases

TABLE 2. *Distribution of the cases with respect to objective classification and age.*

PSG			Age group, yrs 7–14	15–24	25–34	35–44	45–54	55–66	Total	Mean age
AS	0–24		4	4	1	1	2	—	12	23.2
	25–74		2	7	1	1	2	4	17	32.7
	75–133		1	3	1	1	5	3	14	40.1
Total			7	14	3	3	9	7	43	32.5
ASAI	0–49	AI 3	1	—	1	—	1	—	3	30.3
		AI 4	1	—	—	3	2	—	6	37.7
	50–152	AI 3	—	—	1	2	2	1	6	43.5
		AI 4	—	—	2	3	4	—	9	41.7
Total			2	—	4	8	9	1	24	39.7

in the two youngest and in the oldest age groups in AS than in ASAI. The lower incidence of ASAI among the younger patients may be due to the fact that a rheumatic aetiology is more common in ASAI than in AS (see below). It is also conceivable that fewer young patients with ASAI had been transferred to us, since surgical treatment of ASAI was introduced later than of AS. The lower incidence of ASAI in the oldest group may be explained by the poorer prognosis in this condition (see chapter 4), but other factors may also play a part, such as the limited size of the material.

In group AS there was a strikingly uneven age distribution. This may be connected with the selection principles. Among the patients of 7–24 years of age, half were symptom-free and no case was discovered by reason of symptoms, all of them being found during routine examinations common in this age group (e.g. child welfare clinics, school medical examinations, examinations for military service). In the two oldest age groups all had symptoms, for which half of them had sought medical advice, with the discovery of a valvular disorder.

With regard to the *sex* distribution, there were only 7 women in the material (10.4 %), of whom 6 had AS and 1 ASAI. This predominance of men (8.6 : 1) is more marked than in most other series, where, however, varying ratios have been given. In some series a lower ratio of men to women than 2 : 1 has been reported (Contratto & Levine 1937, Karsner & Koletsky 1947, Müller 1956), especially in older patients (Bedford & Caird 1950, Jokipii 1963), while the majority have found a ratio of between 2 : 1 and 4 : 1 (e.g. Christian 1931 b, Kumpe & Bean 1948, Aastrup & Petersen 1952, Olesen & Warburg 1958, Wood 1958). In series of congenital AS a more constant predominance of men is found, with ratios of between 4 : 1 and 5 : 1 (e.g. Nadas 1957, Kjellberg, Mannheimer, Rudhe & Jonsson 1959, Braunwald, Goldblatt, Aygen, Rockoff & Morrow 1963), although in some isolated studies the sex distribution has been equal (Carlgren 1959).

There is thus a predominance of men in

most published series. The degree varies greatly, however, in different series, which may be associated with the selection principles.

Aetiology

A *congenital* aetiology is considered probable on the discovery of valvular heart disease before the ages of 3 or 6 years (Campbell & Kauntze 1953, Marquis & Logan 1955, Downing 1956, Morrow, Braunwald & Sharp 1958, Kjellberg *et al.* 1959), in the absence of a history of rheumatic fever. In this material 7 cases were discovered before the age of 4 years and a further 12 cases before the age of 8 years, without a previous rheumatic history, corresponding to a frequency of a probably congenital aetiology of 33% in AS and 21% in ASAI. If it is considered that cases without known rheumatic fever who are discovered before the age of 20 years have a possibly congenital aetiology (Campbell & Kauntze 1953), this held for 58% of the whole material. In cases diagnosed before 8 years of age, there was an average interval of 14 (range 6–30) years between the discovery and the time of the present investigation at this hospital. In the cases where the interval was long, the originally discovered murmur may have been of physiological nature, which is common in young people and may be mistaken for that of aortic stenosis (Barlow & Pocock 1962, Shabetai 1963).

Aortic stenosis constitutes 3%–6% of all congenital heart diseases (Warburg 1955, Keith, Rowe & Vlad 1958, Carlgren 1959, Kjellberg *et al.* 1959). In some clinical series of aortic stenosis with mixed aetiology, a congenital origin is considered to occur in 12%–20% (Matthews, Medd & Gorlin 1955, Normand 1957, Wood 1958). The higher frequency in this material may be explained by selection, as illustrated by the fact that of the 9 cases from the pediatric clinic only 1 had had rheumatic fever and 7 were diagnosed before the age of 8 years.

Stringent criteria of *rheumatic fever* (cf. Hall 1961) have not been used, since the patients had been treated for this disease at different hospitals, often 15–30 years ago. A history of rheumatic fever was noted in 5 cases with AS and 8 cases with ASAI, corresponding to 12% and 33% respectively. The mean age at the onset of this disease was 17 (range 6–32) years, which conforms with other series (Olesen 1955, Hall 1961). On an average a period of 24 (range 9–41) years had elapsed between the time of the rheumatic fever and the time of investigation at this hospital. In two cases a murmur was reported to have been heard 16 and 18 years, respectively, before the rheumatic fever. At open operation (in the first case) and autopsy (in the second) the aortic cusps were found, however, to be so calcified and deformed that there was no possibility of judging whether any congenital changes were present.

A history of rheumatic fever is found less often among cases with aortic stenosis than among those with mitral stenosis and aortic insufficiency. In autopsy series rheumatic fever has been found in the case history in 11%–27% in AS and in 34%–58% in ASAI (Mitchell, Sackett, Hunzicker & Levine 1954, Müller 1956, Hall 1961, Andersson 1961). In clinical series of AS frequencies of between 12% and 40% have been given (Aastrup & Petersen 1952, Matthews *et al.*, 1955, Baker & Somerville 1959), but the figures are considerably lower

for geriatric patients (Bedford & Card 1960). In a series of patients followed up 20 years after rheumatic fever, ASAI had occurred considerably more often than AS (Bland & Jones 1951). The frequency of this aetiology in the present material thus seems to be similar to that in other series.

A relationship between *hypercholesterolaemia* and aortic stenosis may exist, both according to experimental experience (Mann & Andrus 1956, Munoz & Stephenson 1960) and clinical findings (Cook, Smith, Giesen & Berdoz 1947, Barr, Rothbard & Eder 1954, Boas, Elster & Adlersberg 1954). Serum cholesterol determinations were made on 42 cases in this material. In 2 cases hypercholesterolaemia was found, with a fasting value of more than 400 mg 100 ml in repeated tests. Both were euthyroid men without diabetes, 29 and 38 years old. In one of them a murmur was heard at the age of 7 years, and the other had had rheumatic fever 15 years earlier. In both patients the aortic valves were found at open operation to be greatly calcified, but without any definite difference in degree compared with cases of the same age without hypercholesterolaemia.

A purely *degenerative* aetiology based on atheromatous changes has been discussed previously (Mönckeberg 1904, Sohval & Gross 1936). Such an aetiology is probably uncommon, at least in the age groups occurring in the present material, as will be discussed later in connection with the anatomical findings (page 115). The hypothesis of *brucellosis* (Peery 1958) has been rejected (Griffith & Norris 1961).

Discussion. Apart from the findings at autopsy of changes limited to the aortic valve, the advocates of a degenerative aetiology have also pointed out that rheumatic fever often cannot be traced in aortic stenosis and that this condition is common in older men. Age in itself need not, however, constitute evidence of an atheromatous origin, as "they live longer because they have aortic stenosis rather than have aortic lesions because they are old" (Clawson, Noble & Lufkin 1938). It is possible that patients in the higher age groups do not always remember having had rheumatic fever in their youth, especially if the disease was mild. Furthermore, the predilection of aortic stenosis for older men has been previously overestimated.

Karsner & Koletsky (1947) summarized the earlier discussions on the aetiology, and presented a series of their own in which they considered, on the basis of detailed histological studies, that aortic stenosis was generally caused by rheumatic fever. Since that time the majority of investigators have considered that aortic stenosis usually has a rheumatic aetiology (Mitchell *et al.* 1954, Wood 1958, and others). It has been shown, however, that histological changes of a so-called rheumatic type are not uncommon in cases without macroscopic signs of heart disease, and without a history of rheumatic fever (Hall & Anderson 1943). Even though there is no question of a rheumatic aetiology in the 30–40 % of the cases with mitral stenosis with no history of rheumatic fever, the fact remains, however, that in most series rheumatic fever can be demonstrated in a low frequency in aortic stenosis.

This low frequency of rheumatic fever, and also possibly the predilection of aortic stenosis for men, could be explained by the fact that several of the cases diagnosed after childhood may have a congenital aetiology. Several decades ago Gallavardin (1908, 1930) presented series of cases with aortic

stenosis without a rheumatic history. Although he considered the cause to be some infectious disease, others have discussed the possibility that such cases of aortic stenosis, diagnosed in adult years, may be congenital (Kiloh 1950, Campbell & Kauntze 1953, Stampbach, Wyler, Rentsch & Schüpbach 1961). The occurrence of fused commissures in the majority of cases with AS (see chapter 6), may conform with both a rheumatic and a congenital aetiology. Congenital bicuspid valves may become stenotic later in life (Bacon & Matthews 1959, Edwards 1961 a, 1962).

Conclusions

During a 5-year period isolated aortic disease was found in 25% of cases with aortic and mitral valvular disease. Among the aortic diseases 40% had pure or dominating stenosis, 22% stenosis with insufficiency and 38% pure insufficiency. The groups with stenosis were found to have different age distributions, which may be explained by differences in aetiology and prognosis. There was a marked predominance of men, more marked than in most other series. A probably congenital aetiology was found in 1/3 of the cases with stenosis and in 1/5 of those with combined stenosis and insufficiency. Rheumatic fever, on the other hand, was uncommon in AS but occurred in 1/3 of the cases with ASAI. Hypercholesterolaemia was found in two cases but probably lacked any causal significance.

The opinions on the aetiology of aortic stenosis have varied, as also perhaps the aetiology itself. In the material studied here a congenital origin was common in AS, while rheumatic fever was equally common or more common in ASAI.

CHAPTER 3

HAEMODYNAMIC STUDIES

Introduction

It was not until the last decade that direct studies on the haemodynamics in aortic stenosis were made in man. Previously investigators were restricted to different circulation models and animal experiments. A survey of the haemodynamics in valvular heart diseases has recently been published by Werkö (1962).

Allan (1925) showed in model experiments that it was not until the area of the "aortic valve" had decreased to 25 % of the original that there was a reduction in flow, which could be compensated by increasing the pressure in the "left ventricle" or prolonging "systole". In later model studies (Castenfors, Porjé & Rudewald 1954, Porjé, Philipsson & Ödman 1957) of the relationship between valve area and pressure gradient support was also obtained for older observations (Katz, Ralli & Cheer 1928, Wiggers 1937) that in aortic stenosis the pressure in the aorta lateral to the jet can be considerably lower than the central pressure.

Animal studies have been carried out, as a rule as short-term experiments on an exposed heart with supracoronary stenosis (cf. Straub 1917, Wiggers 1929). Subcoronary experimental stenosis seems to have been used only in studies of the coronary circulation (page 61). It was found at an early date that it was not until the stenosis became pronounced that the pressure in the left ventricle rose, gradually reaching a maximal level which varied in different animals. DeHeer (1912) found a slight pressure rise in the left ventricle and a slight reduction in flow when the valve area had been decreased to 41 %–55 % of the original. The same result was obtained in experimental aortic coarctation (Wiggers 1952). Even at a decrease of the area only to 80 % of the original a distinct increase in weight of the left ventricle after 3–9 months was obtained in experimental coarctation (Wesolowski, Sauvage, Sawyer, Karlson & Fox 1960). In pronounced experimental aortic stenosis, with a valve area of 15 %–20 % of the original, an increase was noted both in the end-diastolic left ventricular pressure and the pulmonary artery pressure (Roy & Adami 1888, Lüderitz 1892, Wiggers 1929).

By mounting human aortic valves in a pulse duplicator the movements and pressure-flow relationships in both normal and stenotic valves have been studied. McMillan, Daley & Matthews (1952) and McMillan (1955) showed in this way that the adult aortic orifice has a triangular surface area of between 2.6 and 3.5 cm^2 during systole. Another important observation was that the systolic area of the stenotic orifice, despite a physiological flow, was smaller in the circulation model, measured on cine images, than on digital palpation. With increasing continuous flow through stenotic aortic val-

ves a linear pressure-flow relationship was found, which was explained by the irregularity of the orifice and the fact that it increased somewhat in size with increased flow (Goodale & Shaw 1955, Kelley, Goodale & Castleman 1960).

A study made by Gorlin *et al.* (1955) constituted a change-over to clinical investigations. With the aid of a pump they studied the pressure-flow relationships in the aortic valves from 3 patients, the cardiac outputs of whom had been measured one year before death. From the given data on the valvular surface area and cardiac output the mean systolic pressure gradient was obtained by a hydraulic formula (Gorlin & Gorlin 1951, Gorlin 1958). They found in this way that, for example, two patients with equally pronounced aortic stenosis (0.4 cm^2) had calculated mean gradients of 31 mm Hg and 151 mm Hg respectively, due to the fact that the mean systolic flows were 93 and 220 ml/syst.sec. respectively. Using the same technique studies were made of both systolic and diastolic gradients and flows in cases of ASAI.

Direct and indirect arterial pulse curves are still used both for quantitative measurements and more qualitative determinations. The correlation between these findings and the objective degree of severity has also been studied, with varying results (Hancock & Abelmann 1957, Lund 1957, Geissler, Porstmann & Albert 1960, Gillmann & Loogen 1960, Epstein & Coulshed 1964, and others). Since nowadays the pressure gradient over the aortic orifice can be measured the study of arterial pulse curves has become of less importance in the evaluation of AS.

When heart catheterization began to be used as a clinical method, different observations were soon made on patients with conditions involving increased work for the left ventricle, such as hypertension and aortic valvular diseases. It was found that these patients with symptoms of failure often had a raised pressure in the right ventricle (Lenègre & Maurice 1947), in the pulmonary artery (Richards 1947, Hickam & Cargill 1947) and in the pulmonary artery wedge position (Lagerlöf & Werkö 1949). The cardiac output was found as a rule to be reduced in left ventricular failure (Howarth, McMichael & Sharpey-Shafer 1946). On the other hand both the pressures in the pulmonary circulation and the flow were normal at rest in asymptomatic patients (Lenègre & Maurice 1947, Werkö & Lagerlöf 1950, Lewis, Houssay, Haynes & Dexter 1953). It was found at a fairly early date that during exercise some patients with normal resting pressures had both a pathological rise in pressure and inadequate increase in the minute volume (Hickam & Cargill 1948, Lewis *et al.* 1953).

Before the method of left ventricular catheterization was available the changes in flow and pressure in patients with aortic stenosis were studied by means of right heart catheterization alone (Goldberg, Bakst & Bailey 1954, Gorlin *et al.* 1955, Yu 1955, Sancetta & Kleinerman 1957, and others). A number of articles have since been published on pressure measurement in the left ventricle in series of patients with AS. These studies will be referred to later, together with the discussion of my own results.

Methods

Left heart catheterization was performed on all cases, in 13 of whom both at rest and during exercise. Right heart catheteriza-

tion was performed at rest on 60 cases and also during exercise in 41 cases.

Right heart catheterization

This was carried out in the customary manner. No serious complications were noted. In one case an arteriovenous aneurysm in the cubital fossa occurred after arterial puncture, and this was resected after arteriography.

Left heart catheterization

During the years in which the material has been collected, different methods have come into use.

Percutaneous *puncture* of the left ventricle (Buchbinder & Katz 1949, Ponsdomenech & Nunez 1951) has been performed with the intercostal technique (Brock, Milstein & Ross 1956). This method was used on 22 cases with AS and 14 with ASAI, and also in a further 2 cases during operation only (see page 26). The technique and complications have been described earlier (Björk & Lodin 1959, Björk, Cullhed, Hallén, Lodin & Malers 1961). In 2 cases signs of haemopericardium were noted after the investigation, and in one of them this had a fatal outcome; at autopsy the left ventricular wall was found to be only a few mm thick at the puncture site, but otherwise about 18 mm thick (page 111). Similar asymmetry is said to be found in the bovine heart (Meyer 1914). Microscopic examination showed no signs of infarction, in contrast to the case described by Fleming, Hancock, Milstein & Ross (1958).

Retrograde catheterization of the left ventricle (Radner 1949, Carlotti, Sicot & Joly 1950, Zimmerman 1950) first came into general use when it was performed with the percutaneous technique (Johnson, Lawlah, McFadden & Dyer 1957, Prioton, Thévenet, Pelissier, Peuch, Latour & Pourquier 1957). In 5 cases with AS and 5 with ASAI an Ödman–Ledin polythene catheter with an end hole and three side holes was introduced percutaneously via the femoral artery. The only complication was arterial thrombosis in one case, after puncture of the exposed artery. Thrombendarterectomy was performed successfully.

Retrograde catheterization was attempted without success in a further 10 cases with AS and 7 cases with ASAI. The ventricle was thus reached in only 10 out of a total 27 cases. A pressure gradient of more than 50 mm Hg was found in 4 of the 10 successful cases, and in 11 of the unsuccessful. Other workers have also reported difficulty in reaching the left ventricle in AS, with successful passage through the aortic valve in 30%–80% of the cases (Voci & Hamer 1960, Gründemann, Bosch, Schwantje, Reijns & Verheugt 1960, Littman, Starobin, Hall, Matthews & Williams 1960, Stampbach *et al.* 1961, Amplatz 1962, Honick, Cayler, Richardson & Taybi 1962, Aker, Friedenberg & Parker 1964).

Transseptal catheterization (Manfredi 1956, Cope 1959, Ross, Braunwald & Morrow 1959) was successfully performed in 16 cases with AS and 5 cases with ASAI. In the beginning we used an Ödman–Ledin catheter, and later a radiopaque teflon catheter with an end hole and 4 side holes, as a rule introduced percutaneously. No complications occurred. In 4 cases the left ventricle was not reached. These cases were investigated before we had had much experience of the method. In 4 of the successful cases the ventricular pressure could only be obtained with a narrow catheter (Cournand 4F or PE 50). In one case, finally, in whom pronounced valvular stenosis was seen at operation, no pressure gradient was found at the first transseptal catheterization, either at rest or during exercise. The investigation was repeated 6 weeks later, when a gradient of 110 mm Hg was found at rest. The heart rate and oxygen consumption were the same on the two occasions (case 28, Table 12). It is probable that on the first occasion the tip of the catheter lay in the mitral valvular plane. In other studies also the left ventricle has not always been reached (Brockenbrough, Braunwald & Ross 1962, Beuren & Apitz 1963 b, Lindeneg, Nielsen & Hansen 1964).

TABLE 3. *The dynamic characteristics of catheters used, as evaluated with a sine-wave pressure oscillator.*

Catheter	Frequency (c/s) to which response was flat within ±5%	Resonant frequency c/s	Approx. degree of damping
Cournand 4F, 100 cm	5	—	0.7
Cournand 8F, 125 cm	13	—	0.6
PE 160, 15 cm[a]	4–8	25	0.5–0.7
Blue Ödman-Ledin radiopaque polythene catheter, 95 cm[a]	20	25–28	0.3–0.4
LV puncture needle[a]	20	24–34	0.3
PE 50, 100 cm[a]	4	—	0.9

[a] The evaluation was performed with connection tubes as used during the catheterization.

Pressure measurements

The intravascular pressures were either measured with a strain-gauge manometer (Swema-Elema) or a manometer of variable inductance type (Elema), connected to amplifier units. The pressure curves and an ECG were recorded on a direct writing four-channel jet recorder (Mingograph 42, Elema). The paper speed was as a rule 25 mm/sec. Mean pressures were obtained by means of electrical integration. Up to 1960 the reference level for zero pressure was a frontal plane through the anterior axillary line, and thereafter a frontal plane 5 cm dorsal to the sternal insertion of the fourth rib was used (cf. Pedersen & Husby 1951, Roy, Gadboys & Dow 1957, Rokseth, Helle, Marstrander & Storstein 1960).

The dynamic characteristics of the catheters used were tested according to principles described by Hansen (1949), with a sine-wave pressure oscillator (Table 3).

Although in some studies the pressure recording apparatus used had very good dynamic properties, with a uniform dynamic response up to 20–35 c/s (Hansen 1949, Holmgren 1956, Kjellberg *et al.* 1959), other workers have found that with the catheter systems usually used a uniform dynamic response of more than 8–12 c/s (Fry, Noble & Mallos 1957) or 16–20 c/s (Piemme 1963) is seldom obtained. In the Fourier analysis of the recorded curves the first three harmonics account for 90% of the total energy of the pressure curve (Porjé 1946) and the first five harmonics for 95% (McDonald 1960). For the measurement of systolic and diastolic pressures a relatively low frequency response should suffice, and Wood, Leusen, Warner & Wright (1954) recommended manometer systems with uniform response of up to 5–10 c/s, followed by a rapid decrease in response, to avoid high frequency artifacts of axial catheter movements. Such artifacts are also found, however, in lower frequencies where they cannot be filtered away (Fry *et al.* 1957, Piemme 1963). Empirically it has been found both in dog experiments and in man that with a uniform dynamic response of up to 5–8 c/s the same pressure values are obtained as with considerably higher frequency responses (Wood 1950, Ellis, Gauer & Wood 1951). In 2 cases of AS the author found that the pressures in the left ventricle and aorta did not change when filters with cut-off frequencies of 70 c/s, 25 c/s, 12 c/s and 6 c/s were used. On the other hand a continuous slowing of the left ventricular maximal rate of pressure rise took place (from about 205 mm Hg/0.1 sec. to about 174 mm Hg/0.1 sec.).

The dynamic properties of the catheter systems used in the present investigation thus

conform with those usually reported in the literature. One exception is the polythene catheter PE 50, which was used in 2 cases for recording the pressure in the left ventricle. The curve in these cases shows a slower rate of pressure rise, and it cannot be excluded that the systolic pressure became too low. For sine-wave like curves the properties were probably sufficient for the calculation of systolic, diastolic and mean pressures, but not for detailed analysis. The pressure curve in the left ventricle is of the transient type and thus has a higher natural frequency, in dogs 10 c/s (Wiggers 1928). It is therefore probable that for the correct reproduction of curves essentially higher demands must be made. Also in support of this conclusion are the high values for the maximal rate of pressure rise which in AS have been measured with intracardiac manometers (Gleason & Braunwald 1962). However, for the recording of systolic and end-diastolic ventricular pressures the technique used is probably adequate.

Normal pressure values were in accordance with those given by Lagerlöf & Werkö 1948, Fowler, Westcott & Scott 1953, Kjellberg *et al.* 1959, and Braunwald, Brockenbrough, Frahm & Ross 1961.

Ventilation and oxygen uptake

The ventilation was determined by evacuating the expiration air from the Douglas bags through a gasometer (Nordgas), and was expressed as the coefficient of ventilation, i.e. the quotient between the ventilation (ml/min BTPS) and the oxygen uptake (ml/min STPD). The normal value is 17–40, on an average 25 (Bartels, Bücherl, Hertz, Rodewald & Schwab 1959).

The oxygen concentration in expired air was determined according to Haldane (Enghoff 1946). On duplicate analyses, the error of a single determination was 0.021 ml/100 ml (0.12% of the mean). Repeated samplings were not carried out (cf. Thomasson 1957, Grabner & Kaindl 1957). The normal values for oxygen consumption were obtained from current tables (Harris & Benedict 1919).

Oxygen saturation and oxygen capacity

These analyses were made with a spectrophotometric method as according to Nahas (Holmgren & Pernow 1959). The error of a single determination for oxygen saturation was 0.30% (0.19% of the mean), and for the haemoglobin concentration 0.18% (1.28% of the mean). Duplicate analyses but not duplicate sampling were made in this material (cf. Thomasson 1957, Holmgren & Pernow 1949).

The normal value for the *arteriovenous oxygen difference* at rest is given as 30–50 ml/l for adults (Eliasch 1952, Thomasson 1957, Holmgren, Jonsson, Levander, Linderholm, Sjöstrand & Ström 1957). The difference is greater in the older age groups (Granath, Jonsson & Strandell 1964).

Cardiac output (CO) and cardiac index (CI)

These were determined according to the direct Fick principle.

$$CO = \frac{\dot{V}_{O_2}}{AVD}$$

where $\dot{V}_{O_2}$ = oxygen uptake (ml/min STPD) and AVD = arteriovenous oxygen difference (ml/l STPD).

In double determinations, which embrace the effect of analysis errors, changes in steady state and biological variations, an error of method of usually 7–10% is found (Eliasch 1952, Thomasson 1957, Grabner & Kaindl 1957, Wade & Bishop 1962). Double determinations during exercise have been published by Holmgren & Pernow (1960). The normal value for the cardiac index is between 2.5 and 5.0 $l/min \cdot m^2$, generally between 3.0 and 4.5 $l/min \cdot m^2$ (distribution curve with positive skewness) (Wade & Bishop 1962). The normal value is highest in the age group 10–20 years (mean 4.3 $l/min \cdot m^2$), decreases progressively and in the age group 60–70 years is on an average 2.7 $l/min \cdot m^2$ (Brandfonbrener, Landowne & Chock 1955, Wade & Bishop 1962, Granath *et al.* 1964).

TABLE 4. *The oxygen saturation of arterial and mixed venous blood, and the arteriovenous oxygen difference at rest.*

Diagnosis		Arter. O_2 sat. %			Mix. ven. O_2 sat. %			AVD, ml/l		
		n	Range	M	*n*	Range	M	*n*	Range	M
AS	I	15	95.1–99.8	97.7	15	68.5–81.7	75.7	15	33.1–53.7	41.4
	II	10	93.3–99.2	96.9	10	61.6–79.5	72.0	10	32.8–64.4	46.1
	III + IV	5	91.4–99.1	95.7	5	47.8–70.2	63.5	5	43.4–76.8	56.2
ASAI	I	4	94.4–99.1	96.3	4	69.5–79.3	74.4	4	32.3–60.4	43.2
	II	5	96.0–100.0	97.3	4	63.5–71.7	67.7	5	40.1–58.9	51.7
	III + IV	3	91.2–96.0	94.1	2	57.4–64.1	60.8	2	61.2–71.8	66.5
AS + ASAI	I	19	94.4–99.8	97.4	19	68.5–81.7	75.4	19	32.3–60.4	41.8
	II	15	93.3–100.0	97.0	14	61.6–79.5	70.8	15	32.8–64.4	48.0
	III + IV	8	91.2–99.1	95.1	7	47.8–70.2	62.7	7	43.4–76.8	59.1

Procedure

The patients were fasted before the investigations. Adult patients were given a premedication of 0.1 g amobarbital (USP) before right heart catheterization, and 5 mg morphine + 0.2 mg scopolamine before puncture or retrograde catheterization of the left ventricle. The arterial pressure was measured by means of a catheter (PE 160) introduced percutaneously according to a modification (Holmgren 1956) of Seldinger's technique (1953). When the pressure in the pulmonary artery wedge position had been recorded, the tip of the catheter was placed in the pulmonary artery. The expired air was collected in a Douglas bag for 10 minutes at rest. In the middle of this period the pressures were recorded and blood samples were taken. In some cases the cardiac output was determined over a period of 2 minutes after puncture of the left ventricle, and over a period of 5 minutes after retrograde catheterization of the ventricle.

A work test was performed in the recumbent position with an electrically braked bicycle ergometer (Holmgren & Mattsson 1954). The patient worked for 6 minutes on each load (Sjöstrand 1947, Wahlund 1948). Pressures and ECG were recorded continuously. The values given for pressures and heart rate during the work test refer as a rule to those measured after 5–6 minutes' work. In those cases where the cardiac output was determined during exercise, this was done during the last 3 minutes of each load.

In 32 cases both right and left heart catheterization were performed on the same day, and in the remaining 28 cases with an interval of usually 2–3 weeks.

The right heart and transseptal LV catheterizations were as a rule performed by the author. The LV punctures were done by V. O. Björk, M.D. or A. Hallén, M.D., and the retrograde LV catheterizations usually by L. Björk, M.D.

Observations at rest

Results

The average *heart rate* was 76 beats/min (range 46–115). It exceeded 100 beats/min

TABLE 5. *Intracardiac pressures, cardiac index and stroke volume in relation to the functional classification, in groups AS and ASAI.*

		AS						ASAI						AS + ASAI					
		I	II	III + IV	II–I	(III + IV)– II	(III + IV)– I	I	II	III + IV	II–I	(III + IV)– II	(III + IV)– I	I	II	III + IV	II–I	(III + IV)– II	(III + IV)– I
RA mm Hg	*n*	21	13	5	—	—	—	5	9	7	—	—	—	26	22	12	—	—	—
	M	3.2	3.9	6.0	+ 0.7	+ 2.1	+ 2.8	2.6	2.7	3.7	+ 0.1	+ 1.0	+ 1.1	3.1	3.4	4.8	+ 0.3	+ 1.4	+ 1.7
	S.E.	0.72	0.93	2.21	1.18	2.40	2.32	1.03	0.87	0.84	1.39	1.20	1.33	0.49	0.65	1.06	0.81	1.24	1.17
	S.D.	3.32	3.35	4.93	—	—	—	2.30	2.60	2.21	—	—	—	2.47	3.07	3.66	—	—	—
PA mm Hg	*n*	21	13	5	—	—	—	5	9	7	—	—	—	26	22	12	—	—	—
	M	15.2	17.0	32.4	+ 1.8	+ 15.4	+ 17.2	18.2	23.6	28.9	+ 5.4	+ 5.3	+ 10.7	15.8	19.7	30.3	+ 3.9	+ 10.6	+ 14.5*
	S.E.	0.65	1.93	9.77	2.03	9.95	9.79	2.09	4.73	6.12	5.16	7.73	6.47	2.15	2.29	5.16	3.14	5.65	5.59
	S.D.	2.96	6.95	21.84	—	—	—	4.67	14.18	16.19	—	—	—	10.95	10.72	17.89	—	—	—
PAW mm Hg	*n*	19	13	5	—	—	—	5	9	7	—	—	—	24	22	12	—	—	—
	M	8.9	8.8	18.2	– 0.1	+ 9.4	+ 9.3	7.0	15.7	19.0	+ 8.7*	+ 3.3	+ 12.0**	8.5	11.3	18.7	+ 2.8	+ 7.4*	+ 10.2***
	S.E.	2.11	1.49	4.92	2.58	5.14	5.35	1.12	3.27	3.69	3.45	4.93	3.86	0.57	1.75	2.83	1.83	3.33	2.87
	S.D.	9.19	5.37	11.0	—	—	—	2.50	9.80	9.76	—	—	—	2.77	8.19	9.81	—	—	—
LV_{ED} mm Hg	*n*	22	14	7	—	—	—	6	11	7	—	—	—	28	25	14	—	—	—
	M	11.0	11.1	17.4	+ 0.1	+ 6.3	+ 6.4*	11.3	19.0	23.3	+ 7.7	+ 4.3	+ 12.0**	11.0	14.6	20.4	+ 3.6	+ 5.8*	+ 9.4***
	S.E.	1.56	1.98	2.62	2.52	3.29	3.05	2.30	2.64	2.61	3.51	3.71	3.48	1.30	1.76	1.96	2.19	2.63	2.35
	S.D.	7.31	7.41	6.93	—	—	—	5.64	8.75	6.91	—	—	—	6.89	8.80	7.31	—	—	—
CI l/min · m²	*n*	15	10	5	—	—	—	4	5	2	—	—	—	19	15	7	—	—	—
	M	4.03	3.37	2.68	– 0.66	– 0.69	– 1.35**	4.23	3.16	2.15	– 1.07	– 1.01	– 2.08	4.07	3.30	2.53	– 0.77*	– 0.77*	– 1.54**
	S.E.	0.25	0.28	0.13	0.37	0.31	0.28	0.60	0.21	—	0.64	—	—	0.23	0.20	0.15	0.30	0.25	0.27
	S.D.	0.96	0.88	0.29	—	—	—	1.21	0.47	—	—	—	—	0.99	0.76	0.46	—	—	—
SV ml	*n*	15	10	5	—	—	—	4	5	2	—	—	—	19	15	7	—	—	—
	M	99.7	75.2	62.0	– 24.5*	– 13.2	– 37.7**	92.3	82.4	41.0	– 9.9	– 41.4	– 51.3	98.1	77.6	56.0	– 20.5**	– 21.6*	– 42.1***
	S.E.	4.93	8.01	8.65	9.40	11.79	9.96	9.18	2.11	—	9.42	—	—	4.29	5.36	7.14	6.86	8.93	8.33
	S.D.	19.08	25.32	19.34	—	—	—	18.36	4.72	—	—	—	—	18.68	20.76	18.89	—	—	—

in 4 cases, none of whom had auricular fibrillation or signs of incompensation.

The *coefficient of ventilation* was low in only one case, a 16-year old boy, for whom a value of 17 was obtained. He had a high oxygen uptake (+65%) and a high cardiac index (5.7 l/min·m²), whereas the AVD was normal (40.5 ml/l). An error of the gas analysis was therefore suspected but could not be proven. A coefficient of over 40 was found in 2 cases (41 and 50 respectively) demonstrating hyperventilation at rest. In both cases the coefficient decreased during exercise.

The average *oxygen uptake* at rest was +24%, expressed as per cent change from the predicted basal uptake. In function class I it was +24% (range −1% to +65%), in class II +23% (−8% to +46%), and in class III+IV +30% (−1% to +67%). Of six cases with an uptake of over +40%, three were in class III+IV. None of these 6 cases, nor any others in this material, had clinical signs of thyrotoxicosis. In 2 cases the BMR was normal before the catheterization, and in another 2 cases, where the BMR was raised, laboratory tests showed the thyroid function to be normal.

The *arterial oxygen saturation* (Table 4) varied between 91.2% and 100.0%, with a tendency to lower values in class III+IV compared with classes I and II. In 6 cases the saturation was less than 95%. All of these had pronounced AS or ASAI, and in 4 of them the pulmonary artery wedge (PAW) pressure was raised (21–29 mm Hg). In the patient with cirrhosis of the liver the saturation was 93.3% and the CI 2.8 l/min·m² at rest.

The *oxygen saturation of mixed venous blood* (Table 4) varied between 47.8% and 81.7%. The mean value decreased with increasing degrees of functional reduction. Five out of 6 cases with a saturation of less than 65% had a raised PAW pressure (18–29 mm Hg).

The *arteriovenous oxygen difference*, AVD, (Table 4) varied between 32.3 and 76.8 ml/l, with higher mean values on increasing degrees of functional reduction. In no case were values of less than 30.0 ml/l obtained, while values exceeding 50 ml/l were noted in 14 cases, with an equal distribution in classes I, II and III+IV. All of these 14 cases were 40 years of age or older, and the mean age was 52 years. All except one (case 33) had pronounced AS or ASAI. Six of them had a raised PAW pressure at rest.

The *cardiac index*, CI, has been given in relation to both the degree of functional reduction (Table 5) and the objective degree of severity (Table 6). The mean values tended to decrease with increasing objective degrees of severity, but these differences were not significant. The differences between the mean values became greater in relation to the degree of disability, and when the whole material was combined they also became significant. A cardiac index of more than 5.0 l/min·m² was found in 3 cases, all of whom were in function class I and between 14 and 16 years old. In 4 cases a CI of less than 2.5 l/min·m² (1.8–2.4 l/min·m²) was noted. Of these, 3 patients were 48–49 years old and one 66 years. All had some degree of functional reduction, and all had pronounced stenosis (peak gradient 49–121 mm Hg). Only one had a raised PAW pressure.

The *stroke volume* has also been given for the two classifications of the material (see Tables 5 and 6). The results are in agreement with those obtained for CI with

TABLE 6. *Haemodynamic findings in relation to the objective classification.*

		AS PSG, mm Hg			ASAI PSG, mm Hg				ASAI Degree AS PSG, mm Hg		ASAI Degree AI	
					0–49		50–152					
		0–24	25–74	75–133	AI:3	AI:4	AI:3	AI:4	0–49	50–152	AI:3	AI:4
	n	10	17	11	3	5	6	7	8	13	9	12
PA mm Hg	M	14.2	18.0	21.9	16.7	22.8	20.3	31.3	20.5	26.2	19.1	27.8
	S.E.	0.62	1.84	4.85	2.20	4.26	6.06	5.95	2.87	4.37	4.00	3.95
	S.D.	1.94	7.58	16.09	3.81	9.53	14.83	15.75	8.12	15.75	12.00	13.68
	n	10	17	11	3	5	6	7	8	13	9	12
PAW mm Hg	M	7.8	10.1	11.6	8.0	13.4	13.5	19.6	11.4	16.8	11.7	17.0
	S.E.	0.95	1.64	2.11	2.08	3.78	5.02	3.09	2.56	2.86	3.42	2.46
	S.D.	3.02	6.76	7.01	3.61	8.44	12.29	8.17	7.23	10.30	10.25	8.51
	n	12	17	14	3	6	6	9	9	15	9	15
LV_{ED} mm Hg	M	10.1	10.2[a]	15.9[a]	7.0[b]	19.5[b]	19.2	20.8	15.3	20.1	15.1	20.3
	S.E.	2.17	1.57	2.21	1.53	3.42	3.61	2.57	3.07	2.04	3.12	1.99
	S.D.	7.52	6.48	8.27	2.65	8.38	8.84	7.71	9.21	7.91	9.36	7.71
	n	7	14	9	2	1	3	5	3	8	5	6
CI l/min · m^2	M	3.9	3.6	3.4	4.6	2.8	3.2	3.1	4.0	3.1	3.77	3.03
	S.E.	0.38	0.29	2.72	—	—	0.90	0.25	0.80	0.33	0.67	0.21
	S.D.	1.00	1.10	8.16	—	—	1.56	0.56	1.39	0.94	1.49	0.51
	n	7	14	9	2	1	3	5	3	8	5	6
SV ml	M	88.7	87.5	79.0	89.5	73	76.7	76.2	84.0	76.4	81.8	75.7
	S.E.	4.00	8.36	8.58	—	—	22.80	8.11	5.69	8.91	12.92	6.65
	S.D.	10.58	31.29	25.75	—	—	39.50	18.14	9.85	25.20	28.88	16.28

[a] and [b]: the differences between the respective means are significant (*). Other differences between means within groups AS and ASAI are not significant. The means in AS group 0–24 mm Hg were compared with those in group 25–74 mm Hg as well as with those in group 75–133 mm Hg.

regard to the mean values in the different groups. A stroke volume of more than 140 ml was noted in one case, a 16-year old boy with a CI of 5.7 l/min·m^2. A stroke volume of less than 50 ml was found in 5 cases, 2 of whom were in function class II (13 and 48 years old) and 3 in class III + IV (46–49 years).

INTRACARDIAC AND ARTERIAL PRESSURES

The *right atrial* (RA) mean pressure (Table 5) was raised, i.e. above 5 mm Hg, in 8 cases, and in 2 of these cases above 10 mm Hg. In none of these 8 cases were signs of tricuspid stenosis observed.

Of the 67 cases in the whole material, 3 had clinical signs of right heart failure, and these 3 had an increased RA pressure. Of the 8 cases with a raised right atrial pressure 6 had a raised PAW pressure and mean pulmonary artery pressure. In the remaining 2 cases with a RA pressure of 10 and 9 mm Hg respectively, the pulmonary artery pressure was normal, while the PAW pressure was slightly raised (15

and 16 mm Hg respectively). These cases also differed from the rest of the material in so far as they, despite the raised PAW pressure, had no functional reduction and remained so during a 2-year follow-up period. In one of them re-catheterization after 2 years showed normal pressures both in the RA and in the PAW position. It is therefore possible that in these two cases the pressure receptor was erroneously placed, or that there may have been other technical errors.

The *pulmonary artery* (PA) mean pressures are shown in Tables 5 and 6. There were no significant differences between the mean values for groups with different objective degrees of severity. When the whole material (AS + ASAI) was classified according to the degree of functional reduction significant differences were found between the mean values for the patients in classes I and III + IV.

The systolic pressure was between 15 mm Hg and 97 mm Hg. It exceeded 35 mm Hg in 13 cases, of whom 7 were in class III + IV. In 12 of these 13 cases the PAW pressure was also raised. All of them had pronounced AS or ASAI.

The mean pressure was between 9 and 68 mm Hg, and above 20 mm Hg in 17 cases, 7 of whom were in class III + IV. The pressure exceeded 25 mm Hg in 12 cases, 11 of whom had a raised PAW pressure.

The *mean pulmonary artery wedge* (*PAW*) *pressure* (see Tables 5 and 6). As for the pulmonary artery pressure, no significant differences were found between groups with different objective degrees of severity. The differences between groups with different degrees of disability were somewhat more marked than for the pulmonary artery pressures. A value of above 13 mm Hg was noted in 2 out of 24 cases in class I. These patients also had raised pressures in the RA, and have been discussed above. In 6 cases out of 21 in class II the pressure was raised, as also in 7 cases out of 12 in class III + IV.

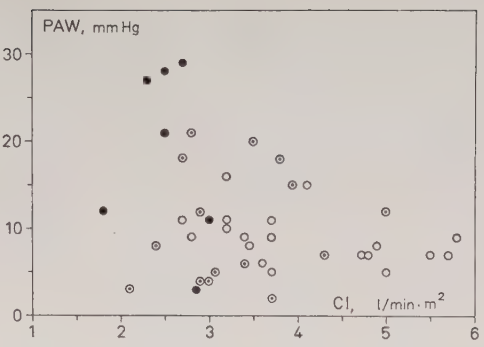

Fig. 1. The relation between the cardiac index (CI) and the mean pulmonary artery wedge pressure (PAW). ○ = class I, ⊙ = class II, ● = class III + IV (AS + ASAI).

The relationship between the PAW pressure and the cardiac index is illustrated by Figure 1. The majority of cases with no functional reduction had both a normal cardiac index and normal pressure, while cases with functional reduction often had a raised pressure and/or a low cardiac index.

Figure 2 shows the relationship between the mean PA and the mean PAW pressures. In addition to the relationship between pressures and degree of disability, an approximately linear relationship is found between the two pressures.

The *pulmonary vascular resistance index*. This was calculated as the quotient (PA–PAW)/CI. The upper normal limit has been given as 3.0 (Holmgren *et al.* 1960). This index was normal in all 19 cases in class I (mean 1.8, range 0.6–2.6), raised in

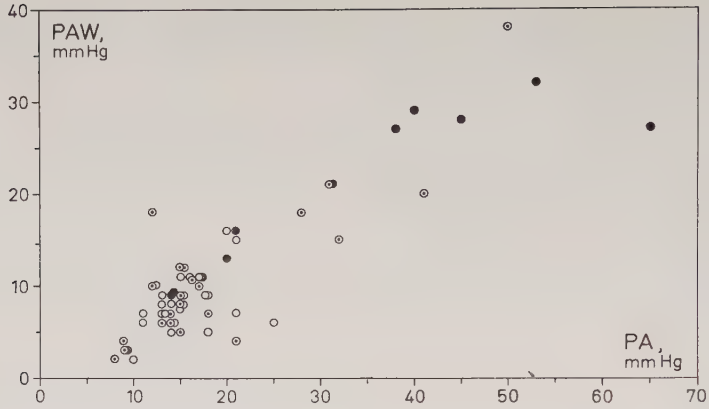

Fig. 2. The relation between the mean pulmonary artery (PA) and pulmonary artery wedge (PAW) pressures. Symbols as in Fig. 1 (AS + ASAI).

8 out of 14 cases in class II (mean 3.4, range 0.6–6.0) and also raised in 4 out of 7 cases in class III + IV (mean 5.5, range 2.0–16.7). For the whole material a mean value of 3.0 was obtained.

The *left ventricular end-diastolic* (LV_{ED}) *pressure* (Tables 5 and 6) showed somewhat better correlation to the objective degree of severity than did the PAW pressure, while the correlation to the functional degree of severity was similar to that of the PAW pressure.

For the patients in whom the PAW pressure was also measured, though as a rule not simultaneously, the relationship between the two pressures is shown in Figure 3. With one exception no patient with a raised PAW pressure had a normal LV_{ED} pressure. On the other hand many patients with a normal PAW pressure had a raised LV_{ED} pressure.

In 19 cases the difference both between the PAW mean pressure and the LV_{ED} pressure, and between the peak of the a-wave in the PAW pressure curve and the LV_{ED} pressure, were determined on simultaneously recorded pressure curves. The mean of the first difference was +2.9* mm Hg (S.E. 1.09 mm Hg). The mean of the second difference was −1.8 mm Hg (S.E. 1.30 mm Hg).

The *left ventricular systolic pressure* varied between 109 mm Hg and 294 mm Hg in group AS and between 142 mm Hg and 279 mm Hg in group ASAI. The variations in relation to the functional classification are shown in Table 7.

The *peak systolic gradient* (PSG) over the aortic orifice was calculated as the difference between the simultaneously measured systolic pressures in the left ventricle and an artery. The arterial pressures were measured in the femoral artery in 31 cases (in particular in ventricular punctures), in the aortic arch in 20 cases and in the brachial artery in 16 cases. The pressure gradient in relation to the functional classification is shown in Table 7. In consideration of the limited size of the material, the degree of stenosis was only divided into three groups for AS and two groups for ASAI.

In two cases (cases 6 and 118), the pressure gradient was measured only during the operation. As is evident by the case histories

(appendix 2), the gradient would probably have been higher pre-operatively.

In order to study the value of measuring the pressure gradient during operation, this gradient was compared with the pre-operative gradient in 11 cases with AS and 12 with ASAI from this material. Two cases had been excluded, one because of a large drop in pressure before the puncture, and the other because of very frequent ventricular extrasystoles during the puncture (cf. Zittel 1960). The pressures were measured in the brachial artery and in the left ventricle by means of puncture, which in 21 cases was performed when the patient had been prepared for extracorporeal circulation, and in 2 cases before closed transventricular dilatation. It was found that in the AS group the gradient was on an average 23.2 mm Hg (range −103 to +43 mm Hg, S.E. 12.5 mm Hg) lower during operation. For the patients with ASAI the mean difference was −30.0** mm Hg (range −60 to +35 mm Hg, S.E. 9.1 mm Hg).

Since the pressure gradient is dependent on the flow, it was of interest to study the effect of left heart catheterization on the haemodynamics. In 10 cases the cardiac output was measured first during right and then during left heart catheterization (see Table 8). In 5 patients, most of them in the younger age groups, considerable changes in cardiac output were found. The Table also shows that the heart rate, and in some cases the oxygen uptake also, may vary regardless of the variations in CO. The method of left heart catheterization, on the other hand, seems to have had little influence. The material was small, however, and the flow measurements during puncture were only performed over a period of 2 minutes. In a larger series of patients where a similar comparison was made, the most marked change appeared to be a reduction of the peripheral resistance (Cullhed & Malers, to be published).

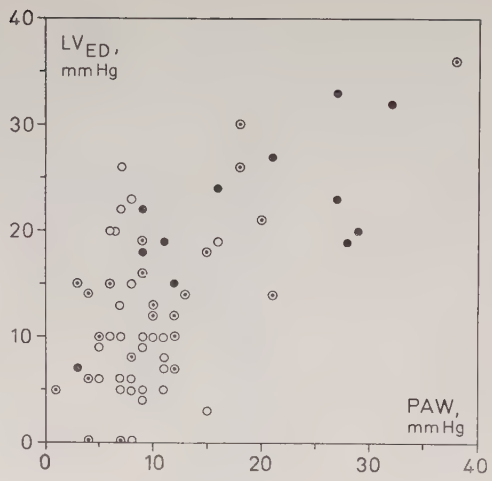

Fig. 3. The relation between the pulmonary artery wedge pressure (PAW) and the left ventricular end-diastolic pressure (LV_{ED}). Symbols as in Fig. 1 (AS + ASAI).

Mechanical alternans, i.e. alternating systolic pressure with regular rhythm, was observed in the left ventricular pressure curves of 5 patients with AS and 2 patients with ASAI (see Table 9). In a further 3 cases, all with severe aortic stenosis, a transitory alternans was observed, in 2 of whom this was seen after a ventricular extrasystole.

As may be seen in the table, there was no relationship with the patient's age or degree of disability. All 7 had had dyspnoea, but only one had had symptoms of left ventricular failure. All had enlargement of the heart, and all except one had negative T waves over the left precordium. The majority had pulmonary hypertension at the time of the recording of alternans. In 2 cases the alternans was only noted during exercise test. All had a high pressure gra-

TABLE 7. *The systolic left ventricular pressure and the peak gradient in relation to the functional classification.*

		Left ventr. peak syst. pressure, mm Hg						Peak syst. gradient, mm Hg					
		I	II	III + IV	II–I	(III + IV)– II	(III + IV)– I	I	II	III + IV	II–I	(III + IV)– II	(III + IV)– I
	n	22	14	7	—	—	—	22	14	7	—	—	—
AS	M	163.0	185.9	232.3	+ 22.9	+ 46.4*	+ 69.3***	39.0	57.2	96.0	+ 18.2	+ 38.8*	+ 57.0***
	S.E.	7.63	11.40	15.26	13.71	19.05	17.06	8.04	9.96	9.27	12.81	13.60	12.29
	S.D.	35.78	42.66	40.37	—	—	—	37.68	37.28	24.54	—	—	—
	n	6	11	7	—	—	—	6	11	7	—	—	—
ASAI	M	170.3	218.5	203.1	+ 48.2*	– 15.4	+ 32.8	26.3	86.4	53.4	+ 60.1**	– 33.0*	+ 27.1*
	S.E.	15.39	8.54	17.36	17.61	19.34	23.20	8.61	12.02	5.90	14.80	13.38	10.44
	S.D.	37.68	28.32	45.94	—	—	—	21.10	39.88	15.62	—	—	—

TABLE 8. *The influence of left heart catheterization on the haemodynamics at rest.*

Case	LHC	HR			$\dot{V}_{O_2}$ ml/l			AVD ml/l			CO l/min			SV ml		
		R	L	Diff. L–R	R	L	Diff. L–R	R	L	Diff. L–R	R	L	Diff. L–R	R	L	Diff. L–R
13	P	55	60	+5	248	358	+110	44.7	46.4	+1.7	5.5	7.7	+2.2	100	128	+28
20	P	76	82	+6	296	437	+141	32.3	33.4	+1.1	9.2	13.1	+3.9	121	160	+39
21	P	66	95	+29	280	407	+127	39.3	38.0	−1.3	7.1	10.7	+3.6	108	113	+5
24	P	73	83	+10	299	340	+41	36.2	57.6	+21.4	8.3	5.9	−2.4	113	71	−42
25	TS	100	93	−7	323	290	−33	36.4	40.4	+4.0	8.9	7.2	−1.7	89	77	−12
26	Re	76	75	−1	245	373	+128	43.8	66.0	+22.2	5.6	5.6	±0	74	75	+1
30	P	97	92	−5	251	256	+5	76.8	70.6	−6.2	3.3	3.6	+0.3	34	39	+5
32	P	72	78	+6	267	286	+19	45.2	49.0	+3.8	5.9	5.8	−0.1	82	75	−7
101	Re	86	91	+5	249	220	−29	33.1	32.2	−0.9	7.5	6.8	−0.7	87	75	−12
123	P	66	75	+9	283	280	−3	49.0	56.4	+7.4	5.8	5.0	−0.8	88	67	−21

R = right, L = left heart catheterization, P = direct puncture, TS = transseptal, Re = retrograde. In case 25 the left heart catheterization was performed two months after the right heart catheterization, in the other nine cases on the same day. Except in case 25 and case 30 a work test was performed prior to the left heart catheterization. Only in oxygen uptake was the mean difference (L–R = +50.6 ml/l) significant (*).

TABLE 9. *Clinical and haemodynamic data in seven cases with mechanical alternans.*

Case	Age	Funct. class	Heart volume ml–ml/m²	Work load kpm/min	HR	Pressures, mm Hg PA	PAW	LV	PSG	CI	SV
14	20	I	890–530	600	158	36	19	315/15	135	8.0	84
28	45	I	1140–600	600	123	43	27	261/21	123	5.8	91
37	53	III	950–560	Rest	85	—	—	205/15	105	—	—
39	55	II	1540–780	Rest	108	—	—	231/29	100	—	—
41	60	III	1440–740	Rest	90	40	29	195/20	60	2.7	58
105	29	II	1360–720	Rest	115	50	38	178/36	70	—	—
122	48	II	1030–560	Rest	100	17	10	231/13	82	—	—

The pressures (PA and PAW) and the cardiac index in case 28 were obtained 6 weeks before the left heart catheterization. However, the same work loads resulted in approximately the same heart rate and oxygen uptake on both occasions.

dient over the aortic orifice. Of these 7 patients 2 died later, 1 after four months and 1 after 18 months.

In a patient with AS who was not included in this material, pulsus alternans was noted 3 seconds after the beginning of a Valsalva manoeuvre (see Fig. 12, page 94).

The *direct arterial pressure* (see Table 10) showed no definite changes in group AS between sub-groups with different pressure gradients. In group ASAI, on the other hand, the diastolic pressure was significantly lower in the patients with AI of grade 4 than in those with AI of grade 3. A diastolic

TABLE 10. *The direct systemic arterial pressure (mm Hg) in relation to the objective classification.*

		AS PSG, mm Hg			ASAI, PSG 0–49		ASAI, PSG 50–152		ASAI Degree AS, PSG		ASAI Degree AI	
		0–24	25–74	75–133	AI:3	AI:4	AI:3	AI:4	0–49	50–152	AI:3	AI:4
	n	12	17	14	3	6	6	9	9	15	9	15
Syst.	M	128.7	136.5	130.2	148.3	157.5	134.8	125.6	154.4[a]	129.3[a]	139.3	138.3
	S.E.	6.49	5.88	7.82	22.36	11.29	6.21	7.97	9.86	5.91	7.92	7.58
	S.D.	22.49	24.25	29.28	38.73	27.66	15.20	23.90	29.58	22.87	23.77	29.36
Diast.	M	75.6	81.9	73.3	81.0	60.1	71.3[b]	55.8[b]	67.1	62.0	74.6[c]	57.5[c]
	S.E.	3.64	4.03	4.22	7.12	6.67	1.84	3.29	5.91	2.89	2.89	3.23
	S.D.	12.61	16.61	15.78	12.33	16.34	4.49	9.86	17.72	11.18	8.68	12.49
Pulse press.	M	53.1	54.6	56.9	67.3	97.3	63.5	69.8	87.3	67.3	64.8	80.8
	S.E.	4.95	3.65	5.61	16.59	9.19	5.43	6.21	9.12	4.26	5.97	6.19
	S.D.	17.15	15.07	21.00	28.74	22.49	13.30	18.63	27.35	16.49	17.92	23.96

[a, b, c]: The differences between these means are significant; [a] (*), [b] (**), [c] (***). The differences between other means within group AS and group ASAI are not significant.

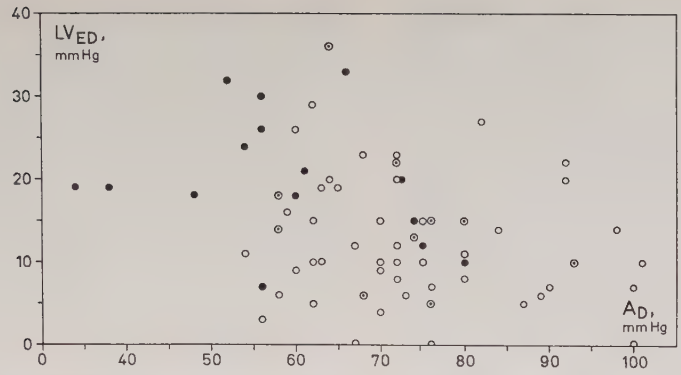

Fig. 4. The relation between the diastolic arterial pressure (A_D) and the left ventricular end-diastolic pressure. ○ = AS, ⊙ – ASAI: 3, ● = ASAI: 4.

arterial pressure of more than 95 mm Hg was recorded in 6 cases with AS (of whom 2 were in class III + IV), but in none with ASAI. A diastolic pressure of below 60 mm Hg was found in 3 cases with AS and 8 with ASAI.

The relationship between the diastolic arterial pressure and the end-diastolic left ventricular pressure, simultaneously measured, may be seen in Fig. 4. It is seen that the cases with the lowest arterial pressure and the highest ventricular pressure, i.e. with the lowest end-diastolic gradient over the aortic orifice, had pronounced AI.

In 23 cases pressures were measured simultaneously in peripheral arteries and the aorta. As a rule the aortic pressure was measured after left ventricular angiocardiography and withdrawal of the catheter. One source of uncertainty is that the tip of the catheter may possibly have lain in or close to the jet (cf. Castenfors *et al.* 1954, Porjé *et al.* 1957, Kjellberg *et al.* 1959). As a rule, however, the tip of the catheter was placed in the middle portion of the ascending aorta, and it should not, therefore, have lain in the ejection jet.

In 15 cases the systolic pressure in the brachial artery was on an average 15.2 mm Hg higher than in the aorta (range −5 to +34 mm Hg). In 8 cases the pressure in the femoral artery was 11.1 mm Hg higher than in the aorta (range −3 to +29).

Discussion

It is desirable that measurements of pressure and flow, in order to be comparable, are made under *basal conditions*. Even the BMR test may influence the factor to be measured (Stern & Ström 1957), the so-called physiologic reactance (Fry 1960). In right heart catheterization the heart rate, cardiac output and pressures can be affected by anxiety and apprehension (for references, see Eliasch 1952, Wade & Bishop 1962). Completely basal conditions are difficult to attain in heart catheterization. The mean value for *oxygen uptake* was the same in this material as in a reported series of normal persons (Holmgren, Jonsson & Sjöstrand 1960). In some cases, however, a high oxygen uptake was observed; half of them belonged to class III + IV where in-

compensation may have contributed to the high uptake (Altschule 1954, Levine & Wagman 1962). In severely disabled cases emotional factors are stated to be of little influence on the haemodynamics (Varnauskas 1955). In the other cases, despite premedication, anxiety and the consequent muscular tension appear to have caused the high oxygen uptake. The raised oxygen uptake found previously in AS (Smith & Levine 1947) was probably due to incompensation or anxiety. Even in the cases with an increased *heart rate,* apprehension was the most probable cause.

The effect of left heart catheterization is of especial interest. In this material large fluctuations in cardiac output were found, and these were most pronounced in the younger patients. The size of the material permits no conclusions to be drawn on the difference in this respect between different methods. With regard to percutaneous ventricular puncture, Klein, as early as in 1930, considered that this method might disturb the basal state too greatly. It was later shown in a series of 9 cases that there were no significant differences between the pressure or flow before and after puncture of the left ventricle (Brock *et al.* 1956). In isolated cases, however, large differences were noted. Similar observations have also been made with regard to transthoracic puncture of the left atrium (Samet, Bernstein, Litwak, Turken & Silverman 1958). It has been maintained by several authors that the transseptal technique does not as a rule change the basal state, over and above the effect of a right heart catheterization (Cope 1959, Ross, Braunwald & Morrow 1960, Bevegård, Jonsson & Karlöf 1961).

The *arterial oxygen saturation* was slightly reduced in some cases, the majority of whom had pulmonary hypertension. Similar observations have been made in mitral stenosis (Eliasch 1952) and hypertension (Varnauskas 1955). In the case with cirrhosis of the liver and a reduced oxygen saturation, there could have been a causal relationship (Abelmann, Calabresi, Kramer, McNeely & Gravallese 1955), but a cardiac index within the low normal limits opposes this view (Murray, Dawson & Sherlock 1958). The *mixed venous oxygen saturation* was especially reduced in cases with pronounced symptoms. The reason for this was probably incompensation, with a high peripheral oxygen uptake compensating the slow flow rate.

The *arteriovenous oxygen difference* did not show markedly low values at rest. In one case (Fig. 9, page 41) the AVD at rest was low in relation to the heart rate, but not extremely low in relation to the oxygen uptake. A relatively high value was seen, on the other hand, in several cases. These patients had pronounced valvular disease and were over 40 years old, which factors may have contributed (Granath *et al.* 1964).

The *cardiac index* was raised in some younger patients, parallel with an increase in oxygen uptake. Since the AVD was not abnormally low, this type of hyperkinetic circulation is not in accordance with "vasoregulatory asthenia" (Holmgren *et al.* 1957). No other causes for increased flow were found.

A low CI was found in the oldest patient in the material. Otherwise a low cardiac index was better correlated to increased functional reduction than to a high pressure gradient, which to some extent may be expected in consideration of the relationship between pressure gradient and flow (see below).

Goldberg and collaborators have found, in a number of studies, strikingly low cardiac output values in AS (Goldberg *et al.* 1954, Goldberg, Dickens, Raber & Hayes 1957, Goldberg, Denton, Bender & Urichio 1958, Raber & Goldberg 1958, Goldberg, Smith & Raber 1958). Since, however, no clinical gradation has been reported it is difficult to evaluate their findings. Furthermore, their normal values are also low (Goldberg *et al.* 1957, 1958 a).

The opposite has been reported by other authors, who have found that many patients have had a large cardiac output (Hancock & Fleming 1960, Braunwald *et al.* 1963). Correlation to the degree of severity of the stenosis has been assumed, and also that the reason for the excess cardiac output is increased coronary flow (Hancock & Fleming 1960). In both of these studies the majority of patients were young, with a predominance of men, which may explain the increased flow (cf. Gorlin, Brachfeld, Turner, Messer & Salazar 1959, Wade & Bishop 1962).

Since in ASAI the measured flow is only a fraction of the total flow, a trend towards lower effective flows in ASAI than in AS could be expected. In this investigation the groups are too small, however, for such a comparison (Table 6).

The author's own findings conform with the experience of other investigators that in AS there is usually a normal cardiac output at rest until the patient has pronounced functional reduction (Gorlin *et al.* 1955, Wood 1958, Dexter, Harken, Cobb, Novack, Schlant, Phinney & Haynes 1958, Wade & Bishop 1962, Bevegård 1962). Lower flows are found in mitral stenosis than in AS, at corresponding degrees of disability (Wade & Bishop 1962).

The *stroke volume* was reduced in some cases with pronounced disability, as has also been reported by Gorlin *et al.* (1955). The correlation between stroke volume and heart volume in the recumbent position, to be found in normal persons (Sjöstrand 1953), is changed in the higher age groups (Granath *et al.* 1964). In a series of patients with AS a reduction in stroke volume in relation to heart volume was found with advancing age. This reduction appeared to be independent of the pressure gradient (Bevegård 1962). A low stroke volume in AS does not thus depend on the stenosis in itself but on other factors such as age, body build, degree of physical training and degree of compensation.

A raised pressure in the *right atrium* was found in all patients who had had symptoms of right heart failure, but also in some other cases, the majority of whom had pronounced AS with increased pressure in the pulmonary artery. Other authors have also found a rise in pressure in the right atrium in cases with AS and pulmonary hypertension (Gorlin *et al.* 1955). Only Goldberg *et al.* (1957) report an increased pressure in some cases without pulmonary hypertension. Increased pressure in the right atrium in AS indicates manifest or latent right heart failure. Although Bernheim's syndrome has been discussed as an explanation for the occurrence of right heart failure in AS (Goldberg *et al.* 1954, Gorlin *et al.* 1955), the findings in the present investigation and those of other authors support the improbability of this mechanism (Selzer, Bradley & Willett 1955).

The pressures in the *pulmonary artery* and the *pulmonary artery wedge* position showed good agreement. This finding does not exclude changes in the pulmonary ves-

sels, such as have been described earlier in cases of left heart failure (Smith, Burchell & Edwards 1954). The occurrence of increased pulmonary vascular resistance in the present material suggests such pulmonary vascular changes. All patients in function class I had normal pressures, as also did 1/3 of those investigated in class II, all with pronounced stenosis. Only one had a normal heart volume (case 2, 11-year old boy). In all patients with a raised pressure the pulmonary vascular resistance index was also raised. It is thus found in AS that even with functional reduction of a moderate degree increased pressures are not uncommon.

Of the greatly disabled patients (class III + IV), only a little over 50% had raised pressures. Both pronounced functional reduction and previous symptoms of left ventricular failure may thus be found despite normal resting pressures. In the few cases in this function class in whom the cardiac index could be measured, this was low: 1.8–3.0 $l/min \cdot m^2$ in those without a raised pressure and 2.3–2.5 $l/min \cdot m^2$ in those with a raised pressure. These findings conform with those of other authors, in AS (Goldberg *et al.* 1954, Gorlin *et al.* 1955). So-called latent left ventricular failure has also been reported in other conditions (Müller & Rörvik 1958, Selzer & McCaughey 1960).

An increase in the *end-diastolic left ventricular pressure* cannot always be regarded as a sign of left ventricular failure (Fisher 1955, Hancock & Fleming 1960). In this material a technical factor probably played some role, since in several cases there was considerable discrepancy between the PAW pressure and the end-diastolic ventricular pressure. In the majority of cases the ventricular pressure was, however, recorded only at low amplification, e.g. with a pressure range of 0–200 or 0–300 mm Hg. The width of the ink line then corresponds to a pressure of up to 5–8 mm Hg. It is possible that the discrepancy sometimes found in other series (Goldberg *et al.* 1958 b, Cosby, Hedge, Amsden & Mayo 1962) may be partly explained in the same way. The diastolic pressure should be recorded with high amplification, e.g. a range of 0–20 or 0–50 mm Hg.

Another contributory cause is the effect of the atrial contraction on the ventricular pressure at the end of diastole. As in mitral stenosis a raised a-wave is found in conditions with left ventricular load (Varnauskas 1955). Although the mean PAW pressure is often raised in cases with AS with a high a-wave (Hancock & Fleming 1960), it may also be normal (Goldberg *et al.* 1957, Braunwald & Frahm 1961). The difference between the LV_{ED} pressure and the PAW mean pressure was probably significant, but not the difference between LV_{ED} and the height of the a-wave. The standard deviations of the two series of differences were approximately equal, suggesting that either of the two PAW pressures may be used as an index of the LV_{ED} pressure. However, this comparison was possible only in a small part of this series. An increase in ventricular volume is seen in connection with the a-wave (Arvidsson 1961). According to Starling's law a stronger ventricular contraction is then possible without increase in the PAW mean pressure (Braunwald & Frahm 1961). Part of the explanation for the deterioration seen in cases with AS on the onset of auricular fibrillation (Mitchell *et al.* 1954, Bergeron, Abelmann, Vazquez-Milan & Ellis 1954) is also to be found here.

Even when the increase in pressure cannot be explained by these two factors, it need not be an expression of left ventricular failure, with the grave prognosis which this implies. In pronounced pulmonary stenosis right ventricular hypertrophy may result in decreased compliance of the ventricle (McCord, Komesu & Blount 1953, Kjellberg *et al.* 1959). It is assumed that increasing age may produce the same result in healthy persons, both in the right and left ventricle (Granath *et al.* 1964), so-called presbycardia. Reduced compliance has also been assumed to occur in hypertrophy of the left ventricle (Gorlin *et al.* 1955, Goldberg *et al.* 1957). In consideration of the usually pronounced myocardial fibrosis, it is doubtful whether these changes are reversible, and whether they can be differentiated from myocardial failure. The correlation between the systolic and the end-diastolic ventricular pressure is, however, poor, both in pulmonary stenosis (Kjellberg *et al.* 1959) and in this and most other series of AS (Dexter *et al.* 1958, Hancock & Fleming 1960, Braunwald *et al.* 1963), although better correlation has also been reported (Fleming & Gibson 1957, Grosse-Brockhoff & Loogen 1964).

Added to these factors are those of a humoral and nervous type which transiently affect the myocardial function and the end-diastolic pressure (Braunwald, Frahm & Ross 1961, Braunwald & Ross 1963).

These factors may explain the fact that a raised end-diastolic pressure in the left ventricle can be recorded both in cases with mild stenosis and in those with negligible symptoms (Goldberg *et al.* 1957, Hancock & Fleming 1960).

The *systolic left ventricular pressure* can rise in AS up to 300 mm Hg, seldom higher,

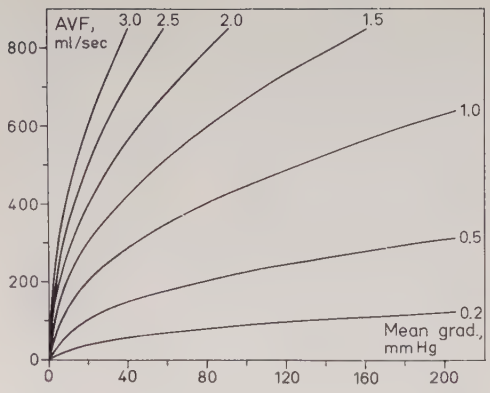

Fig. 5. The relation between the aortic valve flow (AVF) and the mean systolic pressure gradient at different valve areas, according to the formula of Gorlin & Gorlin (1951). A cardiac output of 5.0 l/min will result in a mean systolic flow of about 190 ml/sec. at heart rate 100, and of about 240 ml/sec. at heart rate 60. The corresponding values for a cardiac output of 10.0 l/min are 380 and 480 ml/sec. respectively. For this calculation the systolic ejection period has been calculated according to Fleming & Gibson (1957).

although in exceptional cases a value of 435–500 mm Hg has been noted (Hancock & Fleming 1960). A maximal pressure level has also been found in animal experiments (page 16). The explanation probably lies in the limits of the power of contraction of the myocardial fibres and the possibilities of meeting the oxygen consumption of the myocardium. This has experimentally been found to be proportional to the "tension-time index" (Sarnoff, Braunwald, Welch, Case, Stainsky & Macruz 1958).

The degree of severity of the AS has been expressed in this study as the *peak systolic gradient*. Six cases of AS had a gradient below 10 mm Hg. There was probably no functional stenosis in these cases, which, however, does not exclude slight to moderate anatomic stenosis. In the ASAI group one patient had a gradient below 10 mm Hg

and 9 patients below 50 mm Hg. In consideration of the increased total systolic flow the stenosis was probably mild in these 9 cases, and the pressure gradient was probably partly due to the large total cardiac output (Jonsson 1957).

The pressure gradient, namely, does not depend only on the degree of stenosis but also on the flow, the gradient being proportional to the square of the flow. Since at the same cardiac output the gradient may vary with the heart rate (Blakemore, Schnabel, Kuo, Conn, Langfeld, Heiman & Woske 1957), the systolic flow must be determined. The relationship between pressure and flow in valvular stenoses has been expressed by Gorlin & Gorlin (1951) in the following formula:

$$AVA = \frac{AVF}{C \cdot 44.5 \cdot \sqrt{LV_{sm} - A_{sm}}}$$

where AVA = aortic valve area in cm^2, AVF = aortic valve flow in ml/syst. sec., C = a constant, including C_c, the orifice contraction coefficient, C_v, coefficient of velocity, and a correction factor for mm Hg to cm H_2O ($\sqrt{1.36}$), $44.5 = \sqrt{2g}$, sm = systolic mean pressures, A = arterial. The mean pressures are obtained by means of planimetric integration. The systolic ejection period (SEP) can be obtained from the arterial pressure curve as the time from the onset of pressure rise to the incisura. The systolic flow will thus be:

$$AVF = \frac{CO}{SEP \cdot \text{Heart rate}}.$$

The pressure-flow relationships for different degrees of stenosis, according to this formula, are illustrated in Fig. 5. For slight degrees of stenosis even large increments of systolic flow will result in only a low mean systolic gradient, whereas the opposite is true for a small orifice, where even a small change in flow will markedly influence the gradient, though the flow in maximal degrees of stenosis is restricted.

However, some objections may be raised. Firstly, the coefficient C has been given as 0.9–1.0 on the assumption that the orifice in aortic stenosis is rounded as in pulmonary stenosis (Gorlin & Gorlin 1951, Rodrigo & Snellen 1953). As will be shown later (see page 114) this is seldom true, the orifice being usually slit-like, thus giving a lower C_c and C (the theoretically lowest possible C_c is stated to be 0.5 (Bretting 1960)). Changes in shape of the orifice during systole may account for variations in C_c of 10% (Gorlin *et al.* 1955). Further, with turbulence, which for pulsatile flow through elastic vessels can occur at low Reynold's numbers (McDonald 1960, Ohlsson 1962), the gradient is not proportional to the square but to a higher power of the flow (McDonald 1960).—The systolic ejection period may be difficult to delineate on the recorded pressure curves as the incisura is a relatively high frequency oscillation (cf. McDonald 1960) and may be difficult to differentiate from the systolic vibrations that are often seen in a central arterial pressure curve in AS ("pouls serratique"). The planimetric integration can underestimate the mean gradient, as the maximal rate of pressure rise in AS is high (Gleason & Braunwald 1962) but may be difficult to record with fidelity with long catheters, often with limited dynamic response.

In some series the calculated area has been compared with that found at operation, but in several cases the result has shown disagreement (Fleming & Gibson 1957,

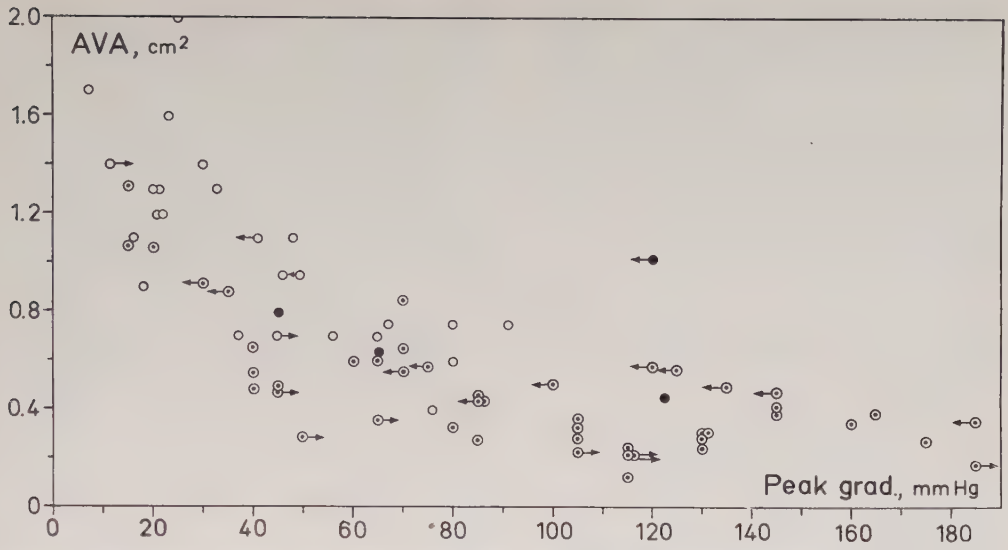

Fig. 6. The relation between the aortic valve area (AVA) and the peak systolic gradient, compiled from published tables, ● = Fleming & Gibson (1957), ○ – Hancock & Fleming (1960), ○ – Tjong & Verheugt (1961). ← = cardiac index exceeding 5.0 l/min.m², → = less than 2.5 l/min.m². The arrows indicate the direction in which the point would be expected to move, should the cardiac index be normalized.

Goldberg *et al.* 1957, Dexter *et al.* 1958, Tjong & Verheugt 1961).

A comparison was made between the peak systolic gradient and the AVA reported for three different series (Fig. 6). With one exception (CO 12.9 l/min) all patients with a peak gradient of at least 50 mm Hg had a maximum valve area of 0.9 cm² and those with a peak gradient of at least 100 mm Hg had a maximum valve area of 0.6 cm². Some relationship was thus found between these parameters. It was also found in these series that the mean systolic gradient was 78–80% of the peak gradient, though the range was wider in the group with gradients of 25–74 mm Hg (S.E. 2.9%) than in that with gradients of 75–124 mm Hg (S.E. 1.9%).

On the basis of these findings an attempt was made to construct, from the same data as in Fig. 6, a "valve index", replacing the mean in Gorlin & Gorlin's formula by the peak gradient, and the measured systolic ejection period by one calculated from the

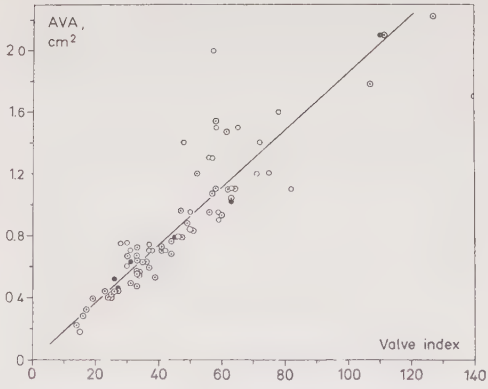

Fig. 7. The relation between the aortic valve area (AVA) and a "valve index" as described in the text. Symbols as in Fig. 6.

TABLE 11. *The peak systolic gradient in relation to the calculated aortic valve area.*

	Peak gradient, mm Hg		
Area, cm²	0–24	25–74	75–133
⩽0.75	—	2	5
0.76–1.50	—	5	1
1.51–2.24	1	1	—
⩾2.25	5	1	—

heart rate, as according to Fleming & Gibson (1957):

$$SEP = 0.31 \cdot \sqrt{R-R} - 0.05$$

where R-R is the length of the heart cycle. The result may be seen in Fig. 7. In spite of the fact that the actual SEP is longer in AS (Katz & Feil 1925, Fleming & Gibson 1957, Gordon, Kirchner & Moscowitz 1961, and others), good agreement is found, especially in the cases with more pronounced stenosis. If the slope for the line in Fig. 7 is calculated, the AVA can be obtained according to the following formula:

$$AVA = \frac{CO}{54.14 \cdot HR \cdot (0.31\sqrt{R-R} - 0.05) \cdot \sqrt{PSG}}$$

or

$$AVA = \frac{SV}{(16.8 \cdot \sqrt{R-R} - 2.7) \cdot \sqrt{PSG}}.$$

In 21 cases in this material, where the cardiac output was measured at the same time as the pressure gradient, this formula was used (see Table 11). In the middle group (25–74 mm Hg) 2 cases with a small valve area were found. The gradients were 71 mm Hg and 49 mm Hg respectively, and the cardiac output values were 4.4 and 3.8 l/min respectively.

In the remaining 22 cases with AS the cardiac output was not measured simultaneously with the pressure gradient. In cases with ASAI the total flow cannot be measured by the methods available.

The cardiac output should always be measured at the same time as the pressure gradient in cases with AS without AI. In cases with a normal cardiac output and an ordinary pulse rate, evaluation of the peak systolic gradient appears to give, for practical use, a satisfactory idea of the degree of stenosis. In other cases it can be of value to calculate the valve area according to the Gorlin & Gorlin formula, or the simplified version given above. In earlier studies the calculated aortic valve area was often used, while in more recent years the use of the peak systolic gradient has been common.

The value of measuring *pressures at operation* for the assessment of operation results has been questioned previously with regard to mitral and pulmonary stenosis (Baden 1955, Lundberg 1958). Many authors have considered that the systolic pressure gradient measured at operation is fairly reliable (Fisher 1955, Brock *et al.* 1956, Glover & Gadboys 1958, Baronofsky, Steinfeld, Kreel, Gordon & Grishman 1959, Baker & Somerville 1959), while others have claimed the opposite (Bailey 1955, Matthews *et al.* 1955, Novack, Cobb, Kuida, Haynes & Dexter 1956). More marked deviations were reported in only 6 out of 30 cases (Baker & Somerville 1959). Factors with influence on the cardiac output during surgery have been discussed by others (Tanenbaum, Braunwald & Morrow 1958). In the majority of the studies referred to above the pressures were measured during short-term closed operations. In my own experience, when the systolic pressure gradient is determined in connection with an open operation the value obtained is too low.

The most common cause of *pulsus alter-*

nans (Traube 1872) is not aortic stenosis (White 1915, 1933). This phenomenon was found in the left ventricular pressure curve in 10% of this material as a whole and in 20% of those patients with a pressure gradient of at least 50 mm Hg. In the two youngest patients it was only observed during exercise. Frequencies of between 25% and 50%, lower for younger persons, have been reported for some other series of AS (Cooper, Braunwald & Morrow 1958, Raber & Goldberg 1958, Hancock & Fleming 1960).

Alternans is seen particularly in cases with a high ventricular pressure, possibly due to interference with the oxygen supply to the myocardium (Cooper *et al.* 1958, Hancock & Fleming 1960). Other factors, such as the diastolic volume of the ventricle and the contractility of the myocardium are also considered to have some influence (Friedman, Daily & Sheffield 1953, Mitchell, Sarnoff & Sonnenblick 1963). Alternans is reported to be less common in AS cases of function class III+IV (Hancock & Fleming 1960), which may be associated with the fact that it is reduced or disappears in incompensation (Ryan, Schieve, Hull & Oser 1955). Alternans has been seen previously to occur during Valsalva's manoeuvre on the simultaneous application of tourniquets (Friedman *et al.* 1953). Simultaneous alternans in the systemic and pulmonary circulation (Ferrer, Harvey, Cournand & Richards 1956) was not observed in the present series. Thus in AS patients alternans occurs among those with a high pressure gradient, and is seen at rest in patients with cardiac enlargement and functional reduction.

The *systemic arterial pressure* showed similar differences between different degrees of AI as in indirect measurement. The changes in blood pressure will be discussed later (see page 68).

The direct pressures were measured in different arteries. It has long been known that the blood pressure varies in different parts of the body (Hürthle 1890). Several studies have shown, however, that the differences between the systolic pressure in the brachial or femoral artery and the central arterial pressure are small, both in persons with no heart disorders and in those with AS (Kotte, Iglauer & McGuire 1944, Kroeker & Wood 1955, Wright 1957, Raber & Goldberg 1958, Roshe & Morrow 1958, Tjong & Verheugt 1960, 1961). It was observed at an early date, however, that in AI there could be very wide variations (Hill 1909, Hill & Rowlands 1911). In large series the mean difference is not great, although in isolated cases it may be considerable (Kotte *et al.* 1944, Wright 1957, Roshe & Morrow 1958, Tjong & Verheugt 1960). In my own material the differences between the central and peripheral arterial pressures were fairly small. Calculations of the aortic valve area have given the same result, regardless of whether the pressure in the aorta or in the brachial artery has been used (Fleming & Gibson 1957, Hancock & Fleming 1960, Tjong & Verheugt 1961).

Observations during exercise

A work test was performed by 41 patients during the right heart catheterization, the size of the load and the duration of the test varying according to the sex, age and degree of disability. In 13 cases a work test was also performed during left heart catheterization. The methods and procedure have been described previously (page 21).

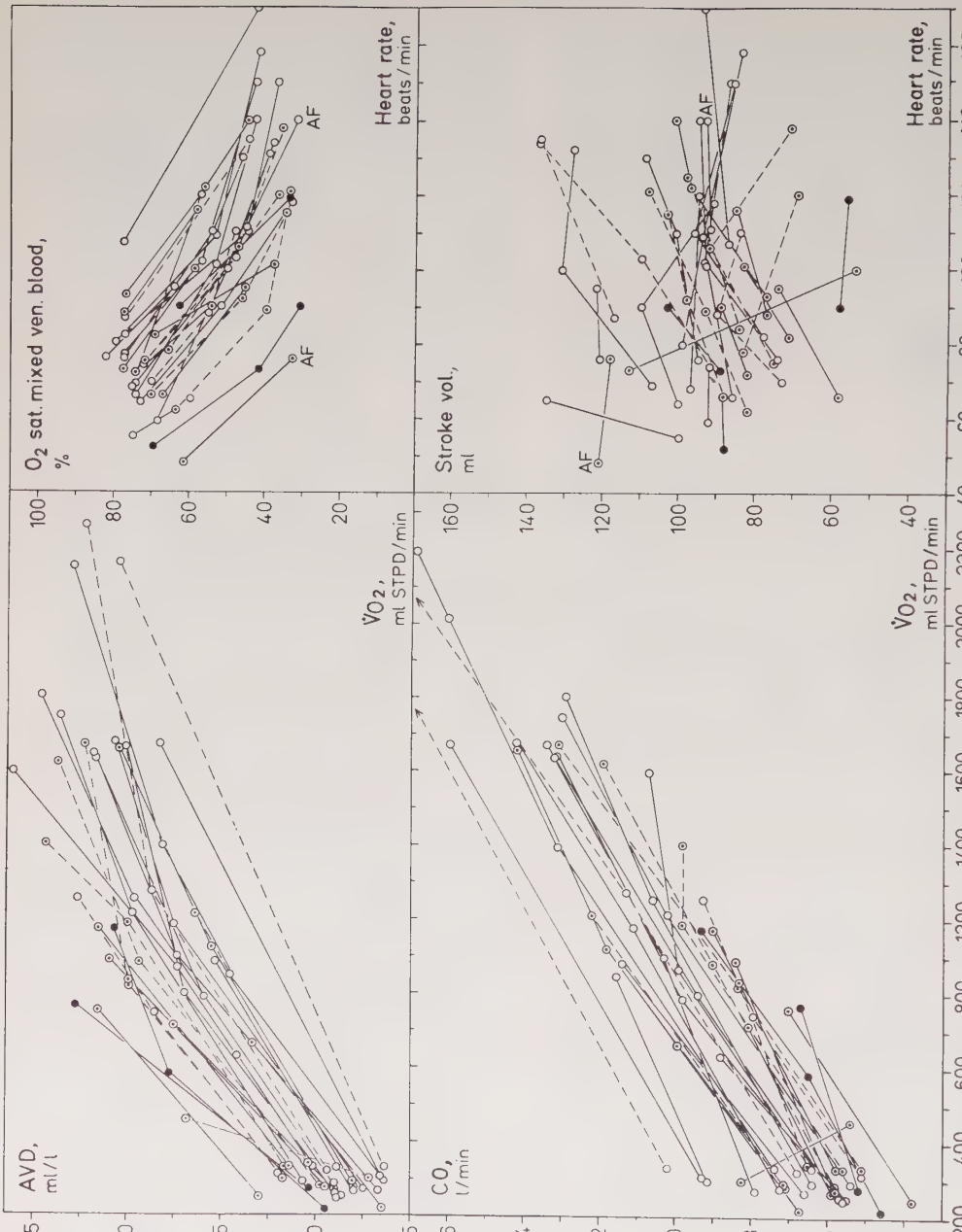

Fig. 8. Left: the arteriovenous oxygen difference (AVD) and the cardiac output (CO) in relation to the oxygen uptake during exercise. The arrows represent points with CO 18.5 and 18.3 l/min, and oxygen uptakes of 1908 and 2059 ml/min, respectively. *Right:* the mixed venous oxygen saturation and the stroke volume in relation to the heart rate during exercise. Symbols as in Fig. 1. ——— = AS, – – – = ASAI. AF = atrial fibrillation.

Work tests were performed less often by both the youngest patients and those with the greatest functional reduction, i.e. in 2 out of 8 cases below the age of 16 years, in 22 cases out of 28 in function class I, in 14 out of 25 in function class II and in 5 out of 14 in function class III + IV. With regard to the objective classification, in group AS work tests were performed in 9 out of 12 cases with a gradient below 25 mm Hg, in 12 out of 17 cases with a gradient of 25–74 mm Hg and in 7 out of 14 cases with a gradient of at least 75 mm Hg. In group ASAI work tests were performed by 7 out of 9 patients with a gradient of below 50 mm Hg, compared with 7 out of 15 with a higher gradient.

Results

The *coefficient of ventilation* decreased during exercise in all cases except one, in whom it increased from 34 to 45.

The *arterial oxygen saturation* varied in most cases within normal limits (Holmgren *et al.* 1960). In 4 cases a reduction of between 4.1% and 6.3% was seen. These cases were equally distributed between the different function classes.

The *mixed venous oxygen saturation* (Fig. 8) decreased during exercise, in the majority of cases in a normal manner in relation to the heart rate (Holmgren *et al.* 1960). One patient (case 5, see Table 12) had a high saturation at rest in relation to the heart rate, and this became normal during exercise. In 2 cases (cases 35 and 36, ages 54 and 56 years, PSG 118 and 52 mm Hg, CI 2.5 and 2.8 l/min·m^2, respectively) the saturation was low at rest and decreased abnormally rapidly during exercise. These two cases had a raised PA pressure at rest. In

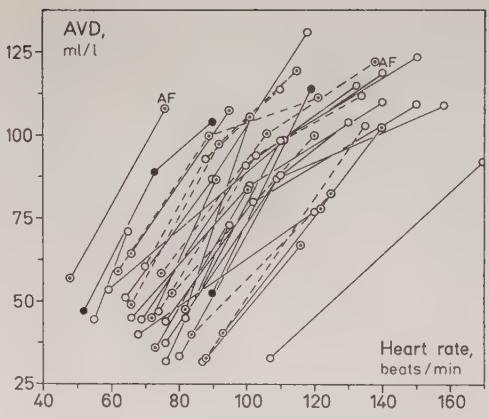

Fig. 9. The arteriovenous oxygen difference in relation to heart rate. Symbols as in Fig. 8.

a further 7 cases the saturation was normal at rest but decreased more rapidly than normally in relation to the pulse rate during exercise, most rapidly in a 60-year-old man. All of these 7 cases had a raised PA pressure during exercise, and in 4 of them it was also raised at rest. In 6 of the 7 cases there was pronounced AS or ASAI.

The *arteriovenous oxygen difference* (AVD) in relation to the heart rate (Fig. 9) was as expected low in one case (case 5) and high in 2 cases (cases 35 and 36). Similarly, in several cases there was a normal AVD at rest, which became abnormally high during exercise. Three of these patients were between 60 and 66 years of age.

In relation to the oxygen uptake (Fig. 8) many patients had a somewhat high AVD, which during exercise did not follow the normal curvilinear regression line (Bevegård, Holmgren & Jonsson 1963). The lowest arteriovenous oxygen differences, both at rest and during exercise, were found in 2 cases (cases 5 and 106, Table 12) where, however, the course of the curve between the only two values obtained was not known. The highest value for AVD at rest

was noted in the oldest patient in the material (66 years) in whom it remained high during exercise. In this patient the PA pressures were normal even during exercise. In 9 other cases the AVD increased from a normal resting value to an abnormally high value during exercise, most rapidly in case 24 (see below). In 5 of these cases there was an increase in the mean PA pressure to at least 25 mm Hg, and in the remainder to between 20 and 25 mm Hg. In a further 5 cases in whom the PA pressure was raised during exercise, the AVD increased normally in relation to the oxygen uptake.

The changes in *cardiac output* (CO) during exercise in relation to oxygen uptake, also considering the functional classification, are shown in Fig. 8. On evaluating the results, these were compared with regression lines with 95 % confidence limits, published by Bevegård *et al.* (1963) for healthy young persons and by Granath *et al.* (1964) for normal older men. The relationship between cardiac output and oxygen uptake is within certain limits rectilinear. It was then found that in class I the cardiac output increased more slowly than normally in 3 out of 15 cases, and in 2 cases it reached a value that was low for the age. In class II a reduced value was reached in 1 out of 11, and in class III + IV the CO increased abnormally slowly in one of the two cases investigated, but did not reach a value that was definitely low for the age (60 years).

In relation to the objective classification it was found that in group AS the CO increased normally in all 7 with a low gradient, despite the fact that the PA pressure rose pathologically in 1 case (case 33, Table 12). In all 10 cases in the group with a gradient of 25–74 mm Hg the CO lay within normal limits but increased abnormally slowly in one case, the case mentioned above in class III + IV. Of the 4 with the highest gradients, one was case 24 (see below). In 2 of the other 3 cases the CO approached the lower 95 % confidence limit, and in the third case was below this limit.

In group ASAI a low value was reached in one of two cases with a gradient of below 50 mm Hg. This patient had AI of grade 4. Of the 6 cases with a gradient of above 50 mm Hg an abnormally low value was reached in only one, where the CO increased normally during the first of the two work loads.

During exercise an abnormally low value was obtained in altogether 3 cases, only one of whom had a PA pressure of more than 25 mm Hg during exercise. In a further 5 cases the CO approached the lower normal limit during exercise, and of these 4 had a raised PA pressure, compared with 8 out of 17 in whom the CO increased within the normal limits and essentially in parallel with the slope of the normal regression line.

In one case (case 24, 32-years old, PSG 109 mm Hg, oxygen uptake 299 ml/min, AVD 36.2 ml/l, CI 5.0 l/min.m^2) a considerably lower CO in relation to the resting value was obtained during a work load of 200 kpm/min (Fig. 8). The patient then continued the work test to 600 kpm/min, when the heart rate in a relative steady state was 160 beats/min. Unfortunately the cardiac output could not be measured during the higher work loads, which were completed with normal pulmonary artery pressures. The pronounced decrease in CO on slight exercise was therefore probably erroneous, due to leakage in the sampling of expired air.

The *stroke volume* (Fig. 8) was un-

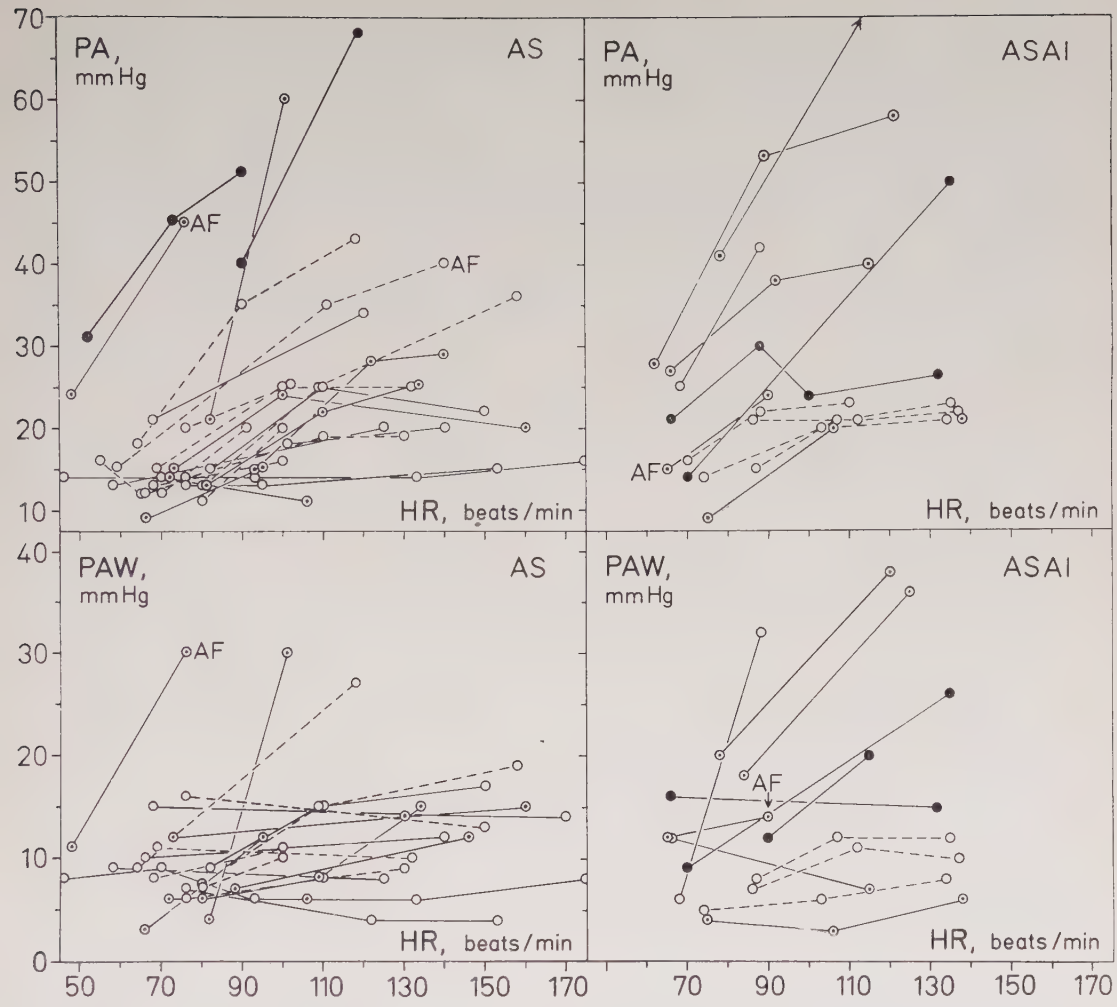

Fig. 10. The pulmonary artery (PA) and pulmonary artery wedge (PAW) mean pressures at exercise. AF = atrial fibrillation. Symbols as in Fig. 1. ○——○ = class I a, ○- - -○ = class I b. The arrow indicates a point with PA pressure 75 mm Hg and heart rate 120 beats/min.

changed in most cases. A pronounced reduction was seen in one patient (case 24, see above) and a reduction of 14–21 ml in 4 patients. This reduction, as also the increase of 20–42 ml which was noted in 6 cases, lies within the normal limits of variation (Holmgren *et al.* 1957, Bevegård, Holmgren & Jonsson 1960).

The *pulmonary artery mean pressure* (see Fig. 10) increased markedly in all patients with a raised resting pressure. In 5 out of 27 cases with a resting pressure of less than 20 mm Hg, the pressure rose during exercise to more than 25 mm Hg. Two of these patients had mild AS (cases 25 and 33, Table 12, appendix 2). In normal persons an increase of the pulmonary artery mean pressure to 25–29 mm Hg during exercise

TABLE 12. *Haemodynamic findings at right and left heart catheterization during work.*

Case No. Sex, age Height, weight cm kg	Work load kpm/ min	HR	$\dot{V}_{O_2}$ ml/min	CO l/min	CI l/min · m²	SV ml	Pressures, mm Hg: LV Syst.	LV End-diast.	System. artery Syst.	System. artery Diast.	PSG	PA	PAW
5, M, 14	Rest	107	306	9.3	5.8	87	125	5	118	63	7	17	9
173, 51	300	170	1471	16.0	10.0	94	177	10	154	98	23	—	—
8, M, 15	Rest	66	256	5.7	3.2	86	120	10	145	75	0	12	10
173, 66	300	101	797	9.4	5.3	93	125	10	115	65	10	18	—
	600	140	1466	13.4	7.5	95	150	10	130	80	20	20	12
11, M, 18	Rest	82	289	6.4	3.7	78	205	10	120	74	85	15	9
172, 62	300	110	1049	10.6	6.1	96	244	9	135	75	109	25	15
	600	150	1600	12.9	7.5	86	288	12	160	100	128	22	17
14, M, 20	Rest	80	268	7.9	4.8	99	215	20	141	92	74	13	7
170, 58	300	109	895	10.3	6.2	94	270	19	170	112	100	25	15
	600	158	1437	13.2	8.0	84	315	15	180	112	135	36	19
15, M, 19	Rest	76	273	7.2	3.6	95	121	10	109	70	12	14	6
185, 77	300	110	978	11.1	5,6	101	146	10	126	78	20	19	8
	600	130	1476	14.2	7.1	109	156	5	130	74	26	19	9
25, M, 38	Rest	93	290	7.2	3.7	77	119	5	135	87	0	15	—
178, 75	300	122	921	11.8	6.1	97	146	5	148	79	0	28	—
	600	140	1456	14.2	7.4	101	148	8	144	70	4	29	—
28, M, 45	Rest	61	305	(6.4)	(3.5)	(100)	225	9	115	70	110	(18)	(9)
180, 69	300	95	921	(9.9)	(5.3)	(110)	258	18	135	87	123	(35)	—
	600	123	1358	(10.7)	(5.8)	(91)	261	21	138	91	123	(43)	(27)
31, M, 50	Rest	69	331	7.4	3.7	107	180	8	170	80	10	15	11
173, 88	400	100	1195	13.1	6.5	131	210	—	205	90	5	25	—
	800	132	1945	16.9	8.4	128	200	—	200	105	0	25	10
33, M, 53	Rest	59	291	5.4	2.7	92	140	7	148	90	0	17	11
186, 74	300	111	1010	10.2	5.2	92	170	8	150	93	20	35	—
	600	140	1546	13.0	6.6	93	180	6	160	100	20	40	—
43, M, 66	Rest	66	245	3.8	2.1	58	167	15	118	70	49	9	3
169, 73	200	95	753	7.0	3.8	74	239	30	140	75	99	17	12
103, M, 31	Rest	74	319	6.8	3.7	92	142	6	124	68	18	14	5
172, 74	400	103	1068	11.3	6.1	110	155	0	130	72	25	20	6
	800	134	2059	18.3	9.8	137	198	4	140	73	58	21	8
106, M, 36	Rest	79	303	(10.2)	(4.9)	(118)	181	15	127	76	54	(15)	(8)
178, 91	400	102	1170	—	—	—	203	18	124	78	79	(21)	(12)
	800	125	1835	(18.5)	(8.8)	(137)	230	14	125	78	105	(23)	(12)
119, M, 49	Rest	62	303	5.1	2.7	82	213	30	156	56	57	28	18
180, 67	300	89	828	8.3	4.5	93	237	18	162	65	75	53	—
	600	121	1468	13.1	7.0	108	252	18	169	68	83	58	—

Table 12 (*continued*)

Case No. Sex, age Height, weight cm kg	Work load kpm/ min	HR	$\dot{V}_{O_2}$ ml/min	CO l/min	CI l/min · m²	SV ml	Pressures, mm Hg: LV Syst.	LV End-diast.	System. artery Syst.	System. artery Diast	PSG	PA	PAW
302, M, 16	Rest	85	307	6.7	3.6	79	197	15	125	90	72	21	11
174, 74	300	122	1070	11.3	6.0	93	229	16	138	98	91	27	17
	600	140	1598	13.6	7.3	97	233	16	135	87	98	30	15
304, M, 20	Rest	78	288	10.9	5.7	140	175	5	128	72	47	24	6
175, 73	300	109	1007	13.1	7.0	120	211	12	147	74	64	37	—
	600	132	1456	14.3	7.7	108	229	8	146	70	83	39	—

The figures within brackets (cases 28 and 106) denote results obtained 6 weeks and 12 weeks earlier, respectively, with the same work loads. Cases 302 and 304 had valvular AS and were operated for aortic coarctation one year earlier.

is sometimes recorded (Jonsson 1957, Holmgren *et al.* 1957, Holmgren *et al.* 1960, Bevegård *et al.* 1963).

The majority of patients in function class I, and also several in class II, had a normal pressure both at rest and during exercise. In 2 cases there was a pathological rise in pressure despite the absence of symptoms. One of these cases was a 16-year old boy (PSG 60 mm Hg), and the other was a patient who denied having symptoms which may have been present (case 109, appendix 2).

The *pulmonary artery wedge pressure* (Fig. 10) was unchanged in most cases, but in 7 cases, most of whom with symptoms, a normal resting pressure rose pathologically during exercise. All patients with a raised PAW pressure during exercise had pronounced AS or ASAI. The two patients in group AS with the highest pressures during exercise were 56 and 60 years old and had a PSG at rest of 52 and 35 mm Hg respectively. Normally the PAW pressure does not rise during exercise. Exceptions are found, however, in persons over 60-years old (Granath *et al.* 1964).

The *pulmonary vascular resistance index* was usually unchanged. It increased in 2 cases, from 5.7 to 8.3 and from 6.0 to 8.4.

The *systolic left ventricular pressure* (Table 12) rose in varying degrees in the majority of cases. In 4 cases, 2 of whom had a low pressure gradient, the increase was negligible in spite of an increase in flow. The highest value obtained was 315 mm Hg.

The *peak systolic gradient,* PSG (Table 12), was below 20 mm Hg at rest in 7 cases, and in only one of these cases did the gradient rise to a maximum of 58 mm Hg, when the effective flow increased from 6.8 to 18.3 l/min. In 8 cases the gradient at rest was between 47 and 110 mm Hg and increased during exercise by an average of 38 mm Hg (13–61 mm Hg). The increase was least pronounced in the case with the highest resting gradient where no increase was observed during the second work load, when the flow did not increase significantly either. Only in 3 cases was a heart rate of at least 150 beats/min reached.

The *end-diastolic ventricular pressure*

(Table 12) was in most cases either unchanged or slightly reduced, and as a rule there was good agreement with the PAW pressure. The end-diastolic pressure rose in 2 cases, but in one of these, however, there was no increase in the PAW pressure.

The *arterial pressure* (Table 12) was measured in the aortic arch in 13 cases, in the brachial artery in 1 case and the femoral artery in 1 further case. The *systolic* pressure increased by at least 10 mm Hg in 5 out of 7 cases with a gradient of below 20 mm Hg, and in 7 out of 8 cases with a gradient of at least 47 mm Hg at rest. In 4 cases the systolic pressure increased by at least 30 mm Hg, and 2 of these had a pronounced gradient at rest. In one case with a low gradient the systolic pressure decreased during exercise. In the 13 patients who performed exercise at two work loads (300 and 600 kpm/min or 400 and 800 kpm/min) the mean increase in systolic arterial pressure from the first to the second load was 5 mm Hg in 6 cases with a resting gradient of below 20 mm Hg, and 6 mm Hg in 7 cases with a gradient of at least 47 mm Hg. No great changes were seen in the *diastolic* arterial pressure.

Discussion

When normal persons perform exercise on an ergometer cycle, a relative steady state with a constant heart rate is usually obtained within a few minutes, except when exercise with the heaviest loads is performed. On increasing loads a linear relationship is found between the work performed and both the heart rate and oxygen uptake. It is only in incompensated patients, or else at very high work loads, that the increase in oxygen uptake cannot be regarded as a measure of the work performed, since part of the energy consumed under these circumstances is obtained anaerobically (Huckabee & Judson 1958). The ability to perform exercise over a fairly long period (e.g. 6 minutes) depends essentially on the oxygen transport capacity. This is partly dependent on the "regulatory capacity" of maintaining a constant stroke volume and regulating the peripheral circulation so that an adequate portion of the cardiac output is directed to the working musculature. Normally there is a linear relationship between the stroke volume, the roentgenological heart volume and the total blood volume (cf. Sjöstrand 1960).

During exercise the left ventricle effectuates a constant stroke volume, with a rising pulse frequency, during which time the systolic period becomes progressively shorter, which means that the mean systolic flow rate increases. In cases with a significant aortic stenosis a prerequisite of the increased flow is a higher systolic pressure gradient over the aortic orifice. The higher systolic ventricular pressure means increased tension in the left ventricular wall. In ASAI the tension is increased further since not only is the pressure higher but the radius of the ventricle greater. Since an increasingly greater portion of the contractile power of the myocardium must be utilized for creating increased tension instead of for fibre shortening, difficulties in maintaining an adequate stroke volume can be expected. This is also shown by the fact that both in cases with left ventricular failure without valvular disorders and in cases of aortic stenosis with normal end-diastolic left ventricular pressure, it is found that the mean systolic ejection rate does not increase during exercise (Levine, Neill,

Wagman, Krasnow & Gorlin 1962). Added to this is the negative effect on the contractile power of the left ventricle which may be exerted by a relative coronary insufficiency. The oxygen consumption of the myocardium is, namely, proportional to the wall tension (Sarnoff *et al.* 1958). The oxygen content in coronary venous blood is normally low, however, and the coronary arteriovenous oxygen difference does not therefore increase during exercise, either in healthy persons (Carlsten, Hallgren, Jagenburg, Svanborg & Werkö 1961) or in patients with valvular heart diseases (Harris *et al.* 1964). Although the most essential coronary blood flow takes place in diastole (Green & Gregg 1940), an increased coronary blood flow is made difficult to a certain extent by the high systolic ventricular pressure in relation to the pressure in the aorta and coronary arteries, added to which is the relative prolongation of systole in AS.

In this material signs of moderately hyperkinetic circulation, i.e. a low arteriovenous oxygen difference and high cardiac output in relation to the heart rate and oxygen uptake, were found in only 2 cases. One of these had mild AS. A large number of the patients, on the other hand, had a tendency to hypokinetic circulation, with a relatively high arteriovenous oxygen difference and a low cardiac output in relation to the heart rate and oxygen uptake. This tendency showed greater relationship to the objective than the functional classification. In the majority of patients, however, it was found that both the arteriovenous oxygen difference and the cardiac output increased according to essentially the same regression lines as in normal persons. Only in 3 cases was an abnormally low increase in cardiac output in relation to the oxygen uptake observed during exercise. In the majority of cases the values lay within the normal limits.

In some earlier series of AS a more pronounced hypokinetic circulation was found (Goldberg *et al.* 1954, Kleinerman & Sancetta 1956). Wade & Bishop (1962) found, however, like the present author, that the majority of patients with aortic stenosis have a normal increase in cardiac output during exercise. Patients with aortic stenosis differ in this respect from those with mitral stenosis, where a considerably smaller increase in flow is found during exercise (Holmgren, Jonsson, Linderholm, Sjöstrand & Ström 1958, Wade & Bishop 1962). On slight steady state work in mitral stenosis, however, the increase in cardiac output is small in only the most incapacitated patients (Werkö 1964). In patients with systemic hypertension an ordinary increase of the cardiac index was found on slight exercise (Varnauskas 1955).

The stroke volume was also essentially unchanged during exercise. In patients with mitral stenosis a decrease in stroke volume on slight exercise was only found in the most incapacitated patients (Werkö 1964), while with greater loads a decrease was seen in the majority of cases (Holmgren *et al.* 1958). Since in my series a heart rate of more than 120–140 beats/min was not as a rule reached during exercise, a reservation must be made for the changes in cardiac output and stroke volume on submaximal and maximal work.

Most patients with aortic stenosis can thus maintain a normal cardiac output and stroke volume during exercise up to a heart rate of 120–140. In all except those with mild stenosis it is found that this takes place at the expense of a considerable in-

crease in the systolic pressure gradient, at least in those in whom the cardiac output increases. Although in several cases with both moderate and pronounced stenosis normal pulmonary artery and pulmonary artery wedge pressures were found during exercise, in some cases, however, there was a pathological rise in pressure during exercise. This applied especially to patients with symptoms, but such rise in pressure was also recorded in isolated asymptomatic cases with pronounced stenosis. A similar discrepancy between subjective freedom from symptoms and haemodynamic signs of left ventricular failure has been observed previously in aortic stenosis under resting conditions (Hancock & Fleming 1960). The question of whether in these cases, with an abnormal increase of pulmonary venous pressure at rest or only during exercise, but with no subjective symptoms, the changes are due to myocardial failure or to a decreased left ventricular compliance, secondary to hypertrophy, cannot be answered.

Because of the age distribution in the present material, consideration must be taken, on evaluating the haemodynamics, especially during exercise, of the changes in the form of a hypokinetic circulation and decreased compliance of the left ventricle, which may be seen in normal persons of the higher age groups (Granath *et al.* 1964). In the 3 cases over 60 years of age who performed the work test, the aortic stenosis was both pronounced and probably of long duration, and the possible effect of age is therefore difficult to assess.

In a previous study of the pressure gradient during exercise in 3 cases of aortic stenosis, it was found that the gradient increased in only one case (Samet, Bernstein & Litwak 1961). The work performed resulted in doubling of the basal oxygen uptake and an increase in flow of 0.23–1.27 $l/min \cdot m^2$. The results of the present investigation show, as expected, that in cases of AS with a significant pressure gradient, this increases with increased flow. The increase in the pressure gradient probably cannot be predicted, however. With very high flow rates the gradient can be expected to increase more rapidly because of turbulence. With mobile cusps the gradient may increase to a lesser extent since the valve area may increase on increasing pressure gradients.

Conclusions

The objective degree of severity of aortic stenosis has been expressed as the peak systolic gradient over the aortic orifice. The choice of artery does not seem to be of great significance, but the central arterial pressure curve seems preferable. In two cases the gradient was only determined during operation after thoracotomy, which probably resulted in an incorrectly low value. The method of left heart catheterization, by its possible effect on the basal state, may have some influence on the size of the gradient. From this point of view the transseptal technique is at present the most suitable. The cardiac output should, however, always be determined simultaneously with the pressure gradient. If the heart rate and cardiac output are within normal limits the peak systolic gradient appears to constitute a sufficiently accurate measure of the degree of severity of the stenosis. In other cases it may be of value to calculate the area of the aortic orifice.

In resting conditions it is found that the

cardiac output and the pulmonary artery and pulmonary artery wedge pressures are better correlated to the degree of functional reduction than to the degree of stenosis or insufficiency, even though normal resting pressures were found in isolated cases in class III + IV. The pressure in the right atrium was raised in the patients who had had symptoms of right heart failure, but also in some other cases, all of whom had a raised pulmonary artery wedge pressure. There was good agreement between the pulmonary artery and the pulmonary artery wedge pressure. On the other hand a raised left ventricular end-diastolic pressure was found in several cases despite a normal pulmonary artery wedge pressure. This may be an error of measurement as the end-diastolic pressure was in some cases recorded with too low amplification. Cases with pronounced functional reduction had, as a rule, a low cardiac output and/or a raised pulmonary artery wedge pressure. The effect of increasing age in normal persons must be considered here. Mechanical alternans was found in some cases. This sign indicates pronounced stenosis. The directly measured arterial pressure showed no correlation to the degree of stenosis, but it did show correlation to the degree of insufficiency in group ASAI.

In a small group of patients where a work test could be performed during LV catheterization, it was found that in cases with a low resting gradient the gradient also remained low during exercise, with one exception, whereas in other cases it increased. In the majority of cases, however, the work test could be performed only during right heart catheterization. In a few cases a slightly hyperkinetic circulation was then found, i.e. a high cardiac output in relation to the oxygen uptake. In most patients the increase in flow followed the slope of the normal regression line, but as a rule, however, it was nearer to the lower normal limit. This is associated with the fact that the increase in the arteriovenous oxygen difference during exercise tended to lie around the upper normal limit in relation to the oxygen uptake, owing to a relatively large reduction of the mixed venous oxygen saturation. Taking into consideration the age distribution of the material, the cardiac output during exercise may be denoted as usually within normal limits in AS and ASAI. In only a few cases, all with pronounced AS or ASAI, the cardiac output did not increase in the normal way. The pulmonary artery and pulmonary artery wedge pressures increased in all patients with a raised resting pressure. In some cases a normal resting pressure increased pathologically during exercise. With a few exceptions, these patients had subjective symptoms. The asymptomatic patients with abnormal pressure increases during exercise all had pronounced AS. They represent cases either with clinically latent left heart failure, or with decreased compliance of the hypertrophic left ventricle. The systolic arterial pressure rose normally during exercise, both in those without and in those with moderate to high pressure gradients.

CHAPTER 4

SYMPTOMS AND SIGNS IN RELATION TO HAEMODYNAMIC FINDINGS

The symptoms and signs in aortic stenosis have been described repeatedly in previous publications. In most of the early works the diagnosis is founded on autopsy or purely clinical findings (for references see Kumpe & Bean 1948). During the last 10–15 years a number of haemodynamic studies on aortic stenosis have been reported. As a rule, however, the different haemodynamic findings have not been related to the clinical symptoms and signs. In the following the relationships between such findings and the subjective symptoms, the physical signs and the electrocardiogram and chest radiogram will be discussed. Finally a multiple regression analysis will be presented, with a number of the individual symptoms and signs as dependent variables.

Subjective symptoms

The first descriptions of symptoms in isolated cases of aortic stenosis verified at autopsy were made in the latter half of the 17th and during the 18th centuries. In 1672 Rayger described sudden death (McGinn & White 1934). Cowper, in 1705, described dyspnoea, orthopnoea and "great faintness and pain about the heart" in a case with AS or ASAI. In 1761 Morgagni described a similar case in whom there were signs of both left and right cardiac failure—"her veins were large". A case of severe AS with a very short symptomatic period before death was described by Stokes (1854).

Right up to the beginning of the 20th century aortic stenosis was regarded as a rare disease of obscure aetiology, benign and well compatible with a long life without symptoms (Osler & Gibson 1915, Lewis 1934). A more distinct picture of the occurrence and clinical signs of the disease appeared later (McGinn & White 1934, White 1937, Scherf & Boyd 1943).

Material and methods

As mentioned previously the material was selective, and there was presumably an underrepresentation both of the completely symptom-free and of the most disabled patients. It is probable, however, that there is a similar selection in most series.

Symptoms occurred in 77% of the patients with AS and in 92% of those with ASAI. Increased tiredness or other vague symptoms have not been included since they are unspecific and only exceptionally occur as initial symptoms (Gillmann & Loogen 1960).

Palpitations: the heart beats more strongly or more rapidly than previously, especially on effort.

Dyspnoea: increased breathlessness on effort.

Chest pain: pain or diffuse discomfort, localized substernally or to one side of the thorax. In this series of patients, when the pain was provoked by physical effort it has been called type I, and when there was no or a doubtful relation to effort, or when it was localized to one shoulder, it has been called type II. The term chest pain is thus not used in the same meaning as angina pectoris (WHO 1959).

Dizziness: as a rule not rotatory, but a more vaguely described sensation, sometimes of the black-out type. Types I and II have the same meaning as for chest pain, with regard to effort.

Syncope: effort syncope. In addition syncope occurred only at rest in 2 cases, in association with venepuncture and a tachycardia attack, respectively.

Left ventricular failure: paroxysmal nocturnal dyspnoea, orthopnoea or pulmonary oedema. Pulmonary oedema had only occurred in one case.

Various so-called cardiac symptoms are not uncommon in healthy persons (Phillips, Chapman & Goerke 1953). The same factors that provoke these symptoms in persons with no objective signs of cardiac disease may be found in cases with organic cardiac lesions. Neither the occurrence nor the degree of subjective symptoms can therefore be expected to have an especially good correlation with the degree of severity of the disease. This is probably particularly true for the symptoms palpitations, chest pain of type II and dizziness of type II, since these symptoms do not increase in frequency with an increasing degree of severity of aortic stenosis (see below).

In 2 cases in this material there appeared to be a considerable functional component (cases 17 and 25, Appendix 2). The clinical picture in these two cases resembles DaCosta's syndrome. The criteria for hyperkinetic circulation ("vaso-regulatory asthenia", Holmgren *et al.* 1957) did not seem to have been fulfilled (cf. chapter 3).

Another fundamental difficulty in investigations of the validity of the symptoms is that of obtaining an adequate case history in children. In the present material, however, there was only one patient below the age of 10 years (case 1, 7 years old). In other cases there may be reason to suspect that symptoms have occurred but have not been mentioned when the case history was recorded (e.g. case 109, Appendix 2).

Results and discussion

A. *The frequency of the different symptoms* (Table 13).

Palpitations occurred in 40 % and 54 % of patients with AS and ASAI respectively.

Dyspnoea was the most common symptom and occurred in 65 % and 80 % (AS and ASAI). This agrees with the results of earlier studies, in spite of the differences in selection principles. In some post-mortem series, for example, dyspnoea is stated to have occurred in 70 %–100 % (McGinn & White 1934, Clawson *et al.* 1938, Dry & Willius 1939 a, Horan & Barnes 1948, Kumpe & Bean 1948, Bergeron *et al.* 1954, Normand 1957). A similar frequency has been reported from clinical studies (Aastrup & Petersen 1952, Matthews *et al.* 1955, Baker & Somerville 1959, Anderson 1961).

Chest pain of type I occurred in 37 % and 63 % (AS and ASAI), and of type II in 19 % and 13 % (AS and ASAI). In 31 cases with chest pain of type I, 20 had angina pectoris proper in so far as the pain, apart from being provoked by physical effort, was of typical localization and char-

TABLE 13. *The frequency of symptoms in relation to the objective and the functional classification.*

Symptom	AS PSG, mm Hg			ASAI PSG, mm Hg				Funct. classif. AS + ASAI		
				0–49		50–152				
	0–24	25–74	75–133	AI : 3	AI : 4	AI : 3	AI : 4	I	II	III + IV
Asymptomatic	5	4	1	—	2	—	—	12	—	—
Palpit. and/or dyspnoea as only symptom	2	2	—	1	—	1	—	5	—	1
Palpit., total	4	8	5	1	4	4	5	7	14	10
Dyspnoea, total	4	12	12	1	3	6	9	10	23	14
Chest pain I, total	2	7	7	1	2	4	8	3	17	11
Chest pain II, total	3	2	3	1	1	1	—	5	4	2
Dizziness I, total	—	5(4)	8(4)	—	—	—	2	3	6	6
Dizziness II, total	3	2	1	—	1	1	1	3	5	1
Dyspnoea + chest pain I or dizz. I	1	7	8	—	2	3	8	3	19	7
Heart failure	—	1	4	1	2	1	2	—	4	7
Total No. of cases	12	17	14	3	6	6	9	28	25	14

Figures within brackets refer to cases with effort syncope.

acter. The question of whether the chest pain in aortic stenosis differs in its clinical type from that in coronary sclerosis has been discussed (Willius 1927, Kumpe & Bean 1948, Matthews *et al.* 1955, Wood 1958). The most important common factor in the chest pain in these two conditions is their relationship to physical effort, to judge by the correlation to the objective degree of severity (see below).

It has long been known that chest pain is more common in AS than in other valvular disorders (Cabot 1926). The frequency has been given previously as between 20% and 50%, both in autopsy series (McGinn & White 1934, Horan & Barnes 1948, Kumpe & Bean 1948, Anderson *et al.* 1952, Bergeron *et al.* 1954, Mitchell *et al.* 1954), and in clinical series (McGinn & White 1934, Contratto & Levine 1937, Dry & Willius 1939 a, Aastrup & Petersen 1952, Matthews *et al.* 1955, Olesen & Warburg 1958). A frequency of 70% and greater has been reported in some recent studies (Baker & Somerville 1959, Hancock & Fleming 1960, Gillmann & Loogen 1960, Anderson 1961). This may be due to the fact that the series of patients had been selected with regard to possible operation, and cases with symptoms were therefore over-represented.

The difference between AS and ASAI as regards the frequency of chest pain of type I was relatively great in the present material. The findings in this respect have varied (McGinn & White 1934, Mitchell *et al.* 1954, Hancock & Fleming 1960). The gradation of AI was probably more certain, however, in this material. Angina pectoris is common even in non-luetic AI (Gallavardin 1930, Segal *et al.* 1956). It is therefore not surprising that cases with ASAI

have a higher frequency of chest pain of type I than those with AS.

Dizziness of type I occurred in 30% and 8%, and of type II in 14% and 13% (AS and ASAI). *Syncope* on effort occurred in 19% (only in AS). Information with regard to the duration of the syncopal attack was available in only one case, where it was stated by witnesses of the attack to be 10–12 minutes. ECG during syncope had not been recorded in any of the cases. A sinus bradycardia with a frequency of 32/min was found in one patient on admission to hospital after syncope. The patient was then fully conscious.

The occurrence of these symptoms in AS, and their relation to physical effort, is well known (Smith 1931, Gravier 1934). Dizziness of this type has been reported as occurring in 10%–30% (AS), and syncope in half this frequency. This applies both to autopsy series (Horan & Barnes 1948, Kumpe & Bean 1948, Bergeron *et al.* 1954, Mitchell *et al.* 1954), and to clinical series (McGinn & White 1934, Marvin & Sullivan 1935, Hammarsten 1951, Leak 1952, Matthews *et al.* 1955, Olesen & Warburg 1958, Swanson 1958), although in a few studies a frequency of 45% has been found (Baker & Somerville 1959, Anderson 1961). Little attention appears to have been paid previously to the remarkably low frequency of dizziness and syncope in ASAI compared with that in AS (Mitchell *et al.* 1954), Dizziness is unusual in pure AI (Segal *et al.* 1956).

Left ventricular failure was recorded in the case histories of 12% and 25% (AS and ASAI). This symptom is of course very commonly found in autopsy series. A frequency of 16%–20% has been reported in some clinical studies on AS patients (Matthews *et al.* 1955, Baker & Somerville 1959). Mitchell *et al.* (1954) stated that the frequency was higher in ASAI than in AS alone.

B. *The degree of severity of the symptoms.* This is often difficult to evaluate. Some idea may be obtained, however, by the occurrence of different symptoms in different degrees of functional reduction (see Table 13). All symptoms except chest pain of type II and dizziness of type II became more common with increasing degrees of functional reduction. Palpitations, dyspnoea and chest pain of type I occurred in practically all cases in functional class III+IV, and dyspnoea in the majority of those in class II. It is my impression that dyspnoea was usually the most disabling symptom in function class III+IV. In a post-mortem study Kumpe & Bean (1948) found that of those patients who had been admitted to hospital for cardiac symptoms, 65% gave dyspnoea as the main symptom and 12% cardiac pain.

C. *The time-course of different symptoms*

INITIAL SYMPTOMS. Seven cases, six below 20 years old, had only one symptom. All of them probably had a congenital aetiology. Of these 7 cases, 3 had dyspnoea and 2 chest pain of type II; these 5 all had mild AS. The other 2 cases had chest pain of type I, and dizziness of type I, respectively. In both patients there was a high pressure gradient, and at operation pronounced stenosis was found. In 20 cases out of 48 with more than one symptom, the first symptom was palpitations or dyspnoea. In the remaining 28 cases these two symptoms first occurred at approximately the same time as chest pain or dizziness.

TABLE 14. *The duration of symptoms in 55 cases.*

Duration years	Symptom, No. of cases					
	Effort dyspnoea	Chest pain		Dizziness		Heart failure
		Exerc.	Rest	Exerc.	Rest	
<1	5	5	2	2	2	2
1–4	21	13	6	9	4	8
5–10	12	9	2	1	3	1
>10	8	3	—	2	—	—
Total	46	30	10	14	9	11

It has been shown previously that young patients with congenital AS are often free from or have few symptoms (Brown 1939, Grishman, Steinberg & Sussman 1947, Marquis & Logan 1955, Downing 1956, Nadas 1957, Braverman & Gibson 1957, Keith *et al.* 1958). In patients with a pressure gradient, however, symptoms are more common (Beuren, Stoermer, Apitz & Hoffmeister 1961, Braunwald *et al.* 1963).

DURATION. This is shown in Table 14. A duration of 1–10 years was found for both dyspnoea and chest pain of type I, while as a rule dizziness of type I and signs of failure were not present for longer periods than 5 years.

Since the majority of patients with pronounced AS or ASAI had undergone operation, no follow-up study of the natural course was possible. Some observations were

TABLE 15. *The course of the disease and the haemodynamic findings in cases with a history of heart failure.*

Case No.	Age years	Case history. Time in years since				Haemodynamic findings				Course (survival time)
		Prelim. diagnosis	Onset dyspnoea	Onset chest pain or dizz. I	Onset heart failure	PSG mm Hg	Grade AI	PAW mm Hg	CI l/min·m²	
30	48	22	14	3	6	121	—	27	2.3	Died (2 months)
34	53	6	6	6	1	78	1	11	3.0	Op.
36	56	36	1	1	½	52	2	21	2.8	Op.
39	55	41	5	—	1	100	—	—	—	Op.
42	63	20	2	20	½	115	—	3	2.9	Alive (1½ years)
112	42	27	5	—	½	19	4	16	—	Died (4 months)
114	44	22	13	13	1	108	3	9	—	Op.
115	46	37	15	5	1	52	4	28	2.5	Died (5 months)
118	49	33	10	10	1	26	4	27	—	Op.
119	49	5	3	—	1	57	4	18	2.7	Op.
120	46	3	3	½	3	16	3	12	—	Op.

made, however, on those patients who had had symptoms of left ventricular failure, and had thus reached a similar stage (see Table 15). A lower mean age was found in the patients with ASAI compared with those with AS. In the majority heart disease had been diagnosed 20–40 years earlier. All had had dyspnoea and the majority had also had chest pain of type I or dizziness of type I for varying lengths of time. The duration of symptoms of cardiac failure, on the other hand, was usually short. In exceptional cases these symptoms were preceded by others for only a short period. In all cases except one there was a high pressure gradient or pronounced AI. Of the 4 patients who were not operated on, 3 died within a few months. The patient who has hitherto survived was the only one of these four who had a normal pulmonary artery wedge pressure. A further 3 patients, who at the time of the investigation had had no symptoms of incompensation, died later. Of the 6 who died, 3 died in cardiac failure and the other 3 suddenly. These 3 latter patients were free from symptoms at rest but otherwise completely disabled. One of them died while driving a car.

Some of the patients who during the period 1958–1962 were referred to this hospital for investigation, died during the waiting time. Autopsy was performed on 15 of these patients, and 7 of them were found to have pure aortic valvular disease. Only 1 of these 7 cases died without having had any symptoms.

This patient was a 16-year old boy (R.W., 361213) who was reported to have been completely free from symptoms. Cardiac roentgenograms revealed nothing abnormal, while ECG 6 months previously showed high voltage and prolonged left ventricular activation time, but normal S–T segments and T waves. He died suddenly on the way to work. Postmortem examination revealed pronounced left ventricular hypertrophy and tight aortic stenosis with calcification.

The occurrence of *sudden death* in aortic stenosis has been discussed, although different definitions have been used (Kumpe & Bean 1948). It would seem appropriate to use the term circulatory arrest to describe the cause of death in those gravely disabled patients who died suddenly without any preceding symptoms of incompensation at rest. This applied to 3 patients in the present material. The term sudden death should then be reserved for those who had died suddenly without any preceding symptoms at all. Used in this sense sudden death is probably uncommon in AS (Schiödt 1956, Braverman & Gibson 1957, Baronofsky *et al.* 1959).

The often long period of time, up to 40 years, from the discovery of a systolic murmur to the onset of symptoms in AS is well known (Herrick 1933, Scherf & Boyd 1943, Anderson *et al.* 1952, Boas 1953, Wood 1958). In a Swedish material it was found that for cases with a rheumatic aetiology the mean interval from the first attack of rheumatic fever up to the time of the first symptom was in AS, ASAI and MS, 35, 29 and 26 years respectively (Hall 1961). The length of time from the rheumatic fever attack to the first symptom of incompensation was found to be 46–48 years, 34–37 years and 28–35 years in AS, ASAI and MS respectively (Mitchell *et al.* 1954, Hall 1961). Even in congenital AS the same slow course is common (Campbell & Kauntze 1953, Marquis & Logan 1955, Downing 1956, Ongley, Nadas, Paul, Rudolph & Starkey 1958) although a tight AS

TABLE 16. *The period of survival after the onset of symptoms in aortic stenosis.*

Author	Total No. of cases	Years after onset of: Dyspnoea Mean	Dyspnoea Range	Angina pectoris (chest pain) Mean	Angina pectoris (chest pain) Range	Syncope (dizziness) Mean	Syncope (dizziness) Range	Heart failure Mean	Heart failure Range
Contratto & Levine, 1937	95	2	—	—	—	¾	—	¾	—
Anderson *et al.*, 1952	49	2.2	0–11	3	¼–15	—	—	—	—
Aastrup & Petersen, 1952	30	7	—	—	—	6	—	—	—
Mitchell *et al.*, 1954	186	—	—	4.1	0–15	3.0	0–15	1.9	0–10
Bergeron *et al.*, 1954	100	—	—	2[a]	—	2[a]	—	—	—
Olesen & Warburg, 1958	18	8.8[b]	1–31	4.7	0–18	3.2	0–12	<1	—
Hall, 1961	59	6.9–8.1[b]	—	—	—	—	—	4.5–4.3	—
Cullhed, 1964	6	10	4–16	6.4	2–16	—	—	1.7	¼–6

[a] Median.
[b] These figures originally referred to the first symptom. In the work of Hall (1961) the two figures for the mean refer to females and males respectively.

may cause death during the first year of life.

The chief explanation for the long asymptomatic period in AS, compared with MS, is probably the pronounced hypertrophy which may develop in the left ventricular myocardium (Peacock 1868). The degree of stenosis also increases gradually, regardless of the aetiology, when the mobility of the cusps decreases by secondary changes in the form of fibrosis and calcification (Hultgren 1948, Edwards 1962). This is also true of congenitally deformed valves without primary stenosis (Osler 1886, Bishop, Bishop & Trubek 1934, Soulié, Matteo, Caramavian, Colonna & Audoin 1960, Edwards 1961 b).

In agreement with the lower mean age at the first onset of symptoms is also the fact that the mean age at death is 47–61 years for ASAI, compared with 60–67 years for AS (Mitchell *et al.* 1954, Normand 1957, Hall 1961). The less favourable prognosis in ASAI is probably associated with the increased left ventricular volume which is as a rule observed in this condition (see page 112). The total work of the ventricle becomes therefore considerably greater (Burch, Ray & Cronvich 1952). A contributory cause may be the higher incidence of rheumatic fever in ASAI, which may result both in an earlier occurrence of valvular thickening and in primary myocardial damage due to myocarditis.

The information that may be obtained from this material on the prognostic significance of different symptoms is the large variation in the duration of symptoms and the serious prognosis when left ventricular failure has been manifested. Some information from the literature is given in Table 16.

D. *Haemodynamic correlations.* The results of *right heart catheterization* (RHC) in groups with different symptoms are shown in Table 17. The symptom-free patients, with a few exceptions, were found to have normal pressures. One third of those patients with symptoms other than those of left ventricular failure had raised pressures

TABLE 17. *Haemodynamic findings in relation to subjective symptoms.*

Symptom	No. of cases	PA, mm Hg				PAW, mm Hg				C I l/min · m²	
		Rest		Exercise		Rest		Exercise		Rest	
		⩽20	>20	⩽25	>25	⩽13	>13	⩽15	>15	<2.6	⩾2.6
No symptoms	12	9	2	4	1	8	1	4	0	0	7
Dyspnoea	47	26	15	8	6	26	14	9	3	6	23
Chest pain I	31	17	11	4	2	18	10	4	2	4	15
Dizziness I	15	9	5	2	2	10	4	3	1	3	7
Syncope	8	5	3	1	2	6	2	2	1	2	5
Heart failure	11	4	6	0	2	4	6	0	1	2	4
No. of cases	67	40	17	13	9	39	15	14	3	6	33

'Exercise' refers to a work load of 250–400 kpm/min; only the results in cases with a normal PA and PAW pressure at rest are presented under this heading.

at rest. Half of those with normal resting pressures had a pathological rise in pressure during exertion. The majority of those with symptoms of left ventricular failure had normal pressures in the right atrium but raised pressures in the pulmonary artery and the pulmonary artery wedge position. Two patients with symptoms of failure but with no pressure rise in the pulmonary circulation had a pathological rise in pressure during exertion.

The cardiac index was normal in the asymptomatic patients and in the majority of those with symptoms. All those with a low cardiac output had at least one symptom, but only 2 out of 6 cases with symptoms of incompensation had an abnormally low flow rate. The oldest patient in the series (case 43, 66 years) had a cardiac index of 2.1 l/min · m². He had several symptoms but not of left ventricular failure. The cardiac output was studied at exercise in 5 out of 8 cases with a history of effort syncope. In no case was the cardiac output abnormally low in relation to the oxygen consumption (Fig. 8).

On *left heart catheterization* (Table 13) it was found that the majority of the asymptomatic patients had a low or moderately high gradient. In 2 cases, however, the gradients were 85 mm Hg and 62 mm Hg respectively.

Palpitations, chest pain of type II and dizziness of type II had no relationship with the pressure gradient. Palpitations or dyspnoea as the only symptom occurred in particular in patients with low to moderate pressure gradients. Dyspnoea occurred in 1/3 of the cases with a low gradient and in practically all those with a high gradient. Dyspnoea combined with chest pain of type I or dizziness of type I occurred almost solely in patients with moderate to high pressure gradients.

Chest pain of type I occurred in 2 cases with low gradients. One of them was case 17 (see appendix 2), and the other a 50-year old man with mild symptoms without any reduction in working capacity. Neither at rest nor during exercise test were there any subjective or objective signs of coronary insufficiency in this patient. The frequency of

chest pain of type I increased with increasing gradients but the difference was not significant.

Dizziness and syncope on effort occurred only with a resting gradient of at least 25 mm Hg, and in higher frequencies with higher gradients (the difference was not significant). Only two patients had chest pain of type I or dizziness of type I without other symptoms. These two patients were young, 13 and 15 years old, and had probably congenital AS, with pressure gradients of 42 and 133 mm Hg respectively.

All patients with AS and symptoms of left ventricular failure had a gradient of at least 60 mm Hg. In group ASAI 5 out of 6 had a high gradient or pronounced AI (grade 4). One exception was found, where the myocardial damage was probably the predominant factor (case 120, Appendix II).

In earlier series very divergent information is found on the relationship of the symptoms to the degree of stenosis observed at autopsy. This holds both for chest pain and dizziness and syncope (Horan & Barnes 1948, Kumpe & Bean 1948, Anderson *et al.* 1952, Bergeron *et al.* 1954, Mitchell *et al.* 1954, Normand 1957).

Even in some series where the patients had been investigated with both right and left catheterization, no correlation was found between different symptoms and haemodynamic data. These series, however, were either small or incompletely reported (Dexter *et al.* 1958, Goldberg *et al.* 1958 a, Abelman *et al.* 1959, Cosby *et al.* 1962).

In other studies the relationship between clinical findings and pressure gradient has been discussed in greater detail. Gillmann & Loogen (1960) classified 52 cases of AS, including 45 valvular, into three equal groups according to the peak systolic gradient (0–40 mm Hg, 41–89 mm Hg and 90–200 mm Hg). The ages were 7–46 years. In these three groups the frequencies of effort dyspnoea were 80%, 90% and 100%, respectively, of chest pain 60%, 80% and 80%, and of dizziness 15–20%. It is not clear whether the chest pain and dizziness were provoked by effort.

Hancock & Fleming (1960) investigated a group with mild AS (10 cases, peak gradient 0–70 mm Hg), a group with moderate-pronounced AS (41 cases, gradient 45–190 mm Hg) and a group with ASAI (10 cases, gradient 25–130 mm Hg). The ages were 5–58 years. Angina pectoris occurred in 30%, 59% and 40% respectively, and syncope in 40%, 37% and 10%. Syncope was thus equally common in the two groups with pure AS, while angina pectoris was more common in the group with the higher gradient. Syncope was uncommon in the ASAI group. When the material was divided into groups with and without angina and syncope, respectively, a higher age, higher systolic left ventricular pressure, higher gradient and smaller valve area were found in the groups with these symptoms. For all haemodynamic parameters, however, there was great overlapping. There was no difference in cardiac index between those with and those without these symptoms.

Braunwald *et al.* (1963) studied a series of 100 cases, 75% of whom were under 20 years of age, with congenital valvular or membranous subvalvular AS. Effort dyspnoea occurred in 16% of the cases with a peak gradient of below 70 mm Hg, and in all cases with higher gradients. Angina pectoris was found in 16% of patients with a gradient of up to 30 mm Hg, in 20% of those with a gradient of 31–70 mm Hg and in 45% of those with a higher

gradient. Syncope on effort did not occur with gradients below 30 mm Hg but was found in 11 % of patients with a gradient of 31–70 mm Hg and in 38 % of those with higher gradients.

A comparison between these three studies and the present material shows a very high frequency of both dyspnoea and angina pectoris in Gillmann & Loogen's series, while dizziness occurred less often than in the other three series. This may be associated with both the principles of selection and the definitions of the symptoms. Dyspnoea, chest pain and dizziness-syncope occurred in a similar frequency in the present material as in that of Braunwald *et al.* In the series of Hancock & Fleming angina pectoris occurred in approximately the same frequency as chest pain in the present material, while syncope, on the other hand, was strikingly common, even in cases with a low gradient. It is possible that syncope not provoked by effort was also included. The low frequency of dizziness and syncope on effort in ASAI agrees with the findings of Hancock & Fleming.

E. *Pathogenesis of symptoms.* Of the patients who had had dyspnoea on effort, one-third had normal haemodynamic values at rest. Two factors in particular may explain the lack of agreement between the occurrence of dyspnoea and the haemodynamic findings on RHC. Firstly, as in the majority of earlier studies, gradation of the degree of severity of the dyspnoea was not considered possible. Secondly, it is possible that significant changes would have been noted in the majority of the patients, if during RHC the patients had been allowed to perform for them maximal physical work. It is, however, hardly probable that this would hold for all cases with dyspnoea, since this symptom may be found in patients with no or only mild cardiac disorders. Furthermore, our knowledge of the factors that provoke dyspnoea is incomplete (Cherniack & Cherniack 1961). Reduction in ventilation capacity did not explain the occurrence of dyspnoea in the present material.

The ventilation capacity was investigated in 24 cases, by means of a spirometer of Bernstein type (Kifa-Spirokombi). The following lung volumes were determined: vital capacity (VC), forced expiratory volume during one second ($FEV_{1.0}$), forced vital capacity (FVC), expiratory flow index ($FEV_{1.0}$ in per cent of FVC), and the maximum voluntary ventilation at free respiratory rate (MVV_F) and at a respiratory rate of 40 per minute (MVV_{40}). In 15 cases the maximum expiratory flow rate (MEF) was determined with a Wright's peak flow meter. The values were expressed in BTPS. Normal values were used according to Berglund, Birath, Bjure, Grimby, Kjellmer, Sandqvist & Söderholm 1963, Grimby & Söderholm 1963 and Birath, Kjellmer & Sandqvist 1963. 15 out of the 24 cases had experienced dyspnoea on effort and some degree of disability (NYHA II–IV). In 7 of these 15 dyspnoeic cases an increased mean PAW pressure at rest was found. These 7 cases included the only patient with signs of a moderate restrictive limitation in ventilatory function:

Case 115, 40-year-old woman, height 159 cm. VC: 2.0 l, $FEV_{1.0}$: 1.4 l, FEV%: 72%, MVV_F: 58 l, MVV_{40}: 52 l.

It has been confirmed that the most common cause of *chest pain* in significant aortic stenosis is not coronary sclerosis (Christian 1931 b, Tuohy & Eckman 1931, Boas 1935, Contratto & Levine 1937, Friedberg & Sohval 1939, Horan & Barnes 1948, Kumpe & Bean 1948, Bergeron *et al.* 1954, Mitchell *et al.* 1954, Schiödt 1956). Only exceptionally has the opposite been reported

TABLE 18. *The distribution of coronary arteriosclerosis and myocardial fibrosis in relation to age, sex, the presence of chest pain, the pressure gradient and the heart weight.*

Case	Age	Sex	Chest pain		PSG	Heart weight, g	Coronary arteries		LV myocardium	
			I	II			Scler.	Occl.	Fibrosis	Infarcts
10	16	M	–	–	133	270	0	0	0	—
24	32	M	+	–	109	510	0	0	+	0
28	45	M	–	+	110	820	0	0	+ +	0
30	48	F	+	–	121	540	0	0	—	0
32	49	M	–	+	49	450	0	0	+ + +	0
34	53	F	+	–	78	500	+	0	+ +	0
35	55	M	+	–	118	530	0	0	+ +	Small
36	56	M	+	–	52	800	+ +	0	+ +	0
38	55	M	–	+	75	—	0	0	+ + +	0
39	55	M	–	–	100	1150	—	0	+ + +	0
41	61	M	+	–	60	580	+ + +	+ +	+ + +	Small
105	30	M	+	–	70	770	0	0	+ +	0
106	37	M	–	+	54	940	0	0	+ +	0
107	36	M	+	–	145	920	(+)	0	+	0
109	42	M	–	–	49	875	0	0	+ + +	0
113	45	M	+	–	152	900	+ +	0	+ +	0
114	47	M	+	–	108	730	+	0	+ + +	Small
115	47	F	+	–	52	690	+	0	+	0
116	45	M	+	–	116	750	0	0	+ +	0
117	47	M	+	–	10	760	+ +	+	+ + +	Large
118	49	M	+	–	26	790	0	0	+ + +	0
121	50	M	–	–	105	800	+	0	+ + +	Small
123	55	M	+	–	77	700	0	0	+ + +	0

The degree of coronary arteriosclerosis and myocardial fibrosis was arbitrarily graded from + to + + +. In case 117 a large recent myocardial infarction was found. The patient died of septicaemia 3 weeks after surgical repair.

(Mathivat, Lembessis & Paulon 1951). It has even been claimed that the coronary arteries are protected from arteriosclerosis by the aortic stenosis, in the same way as the abdominal aorta in aortic coarctation (Ask-Upmark 1942), so that a smaller degree of coronary sclerosis is found than is normal for the age (Horan & Barnes 1948, Bergeron *et al.* 1954, Snellen, Hartman & Hahn 1961).

Autopsy was performed on 25 cases in the present material. For 23 of these cases information was given on the condition of the coronary arteries (see Table 18). Mild coronary sclerosis was found in one case out of 8 without chest pain of type I. Of 15 cases with chest pain of type I, 8 had coronary sclerosis. This was pronounced in 4 cases, 2 of whom had distinct luminal constriction. In 3 of these 15 patients small localized fibrotic changes were seen.

Thus in this series also it appears to have been only exceptionally that coronary sclerosis caused chest pain. Moderate coro-

nary sclerosis was, however, more common in the older patients. Chest pain in AS is probably due to relative coronary insufficiency (Büchner 1934), where the coronary flow in itself is normal but not sufficient in relation to the increased left ventricular work (Contratto & Levine 1937, Hultquist 1941). As shown in the present material also, pronounced fibrosis may be found even though the coronary arteries are normal.

Measurements of the coronary blood flow in experimental valvular short-term stenosis of the aortic orifice have shown conflicting results (Green 1936, Blumenthal, Wang & Wang 1962). Only a few studies have been made on patients with AS, and these have shown a normal flow (Bing, Hammond, Handelsmann, Power, Spencer, Eckenhoff, Goodale, Hafkenhield & Kety 1949, Read, Porter, Bond & Bradford 1955, Blain, Schafer, Siegel & Bing 1956). A normal flow has also been found in AI, with the exception of those patients with angina pectoris (Bing *et al.* 1949, Regan, Talmers, Christensen, Wada & Hellems 1956).

Dizziness and *syncope* have been considered to be due to cerebral ischemia on failure of the left ventricle (Smith 1931). This is contradicted to a certain extent by the fact that the haemodynamic findings in patients with syncope do not differ from those in cases without, either in the author's own material or those of others (Hancock & Fleming 1960). Marvin & Sullivan (1935) presented the hypothesis of a hypersensitive carotid sinus, which, however, has been rejected (Contratto & Levine 1937, Mitchell *et al.* 1954). In some cases ECG was recorded before and during syncope, and it was found that syncope usually was followed by mild arrhythmia in the form of nodal rhythm or sinus bradycardia; in one case, however, it occurred simultaneously with asystole (Hammarsten 1951, Leak 1952). Asystole or ventricular fibrillation is not probably therefore the most common cause. In some cases with AS and total atrioventricular block, syncope did not occur (Gravier 1934). This to some extent opposes the view of total block as a cause of syncope in AS.

Direct measurement of the cerebral blood flow in cases with AS has shown a decreased blood flow at rest (Bodechtel 1954), and in another study increased cerebral resistance during exercise (Kleinerman & Sancetta 1956). These results have been criticized, however (Lassen 1958). In a later study decreased cerebral blood flow in AS was only found in cases with incompensation (Bernsmeier, Gottstein & Rudolph 1964).

It is possible that syncope in aortic stenosis may be due to peripheral vasodilatation, such as in the skeletal musculature on physical effort, in combination with a fixed cardiac output. Contratto & Levine (1937) found among patients with AS that those with a history of syncope had a lower blood pressure than those without. On emotional stimuli a reduction of the diastolic blood pressure may be found in patients with AS, in contrast to those with AI (Gorlin & Goodale 1956). Afferent impulses in a vasomoter reflex such as this may arise from the left ventricle (Sharpey-Schaffer 1960). Where these receptors are situated and what it is that provokes the reflex is unknown. It is claimed that such vasodilatation is inhibited by pulmonary capillary congestion, as in mitral stenosis (Daley 1957). Syncope is not observed in incompensated patients, which has been considered to be connected

with the increased residual blood volume (Sharpey-Schaffer 1960). A similar mechanism could then explain why syncope is found so rarely in cases with AI and ASAI, even in those with pronounced stenosis.

Conclusions

So-called cardiac symptoms occur both in persons with no objective signs of cardiac disease and in those with mild heart disorders. It was therefore not unexpected to find in this material cases with pronounced symptoms in spite of the mild nature of their disease. The reverse also occurred, especially in younger patients.

Of the different symptoms in this series chest pain and dizziness, when not provoked by effort, had no relation to the objective degree of severity. In cases of AS an attempt should therefore be made to determine the relationship between these symptoms and effort.

Dyspnoea, chest pain and dizziness, provoked by effort, were related to the objective degree of severity as also were symptoms of left ventricular failure. All of these symptoms, except dizziness and syncope on effort, were more common in ASAI than in pure AS. This is related to the more unfavourable prognosis in ASAI.

Dyspnoea on effort was the most common symptom, and as a rule was predominant and also the first symptom. The survival time after the onset of dyspnoea appears to be on an average 8 years, although with wide ranges. Dyspnoea occurred in one third to one half of the cases with mild AS or ASAI, and in the majority of cases where this was pronounced. Combined dyspnoea and chest pain or dizziness on effort occurred, on the other hand, only in moderate-pronounced AS or ASAI. Raised pressures in the pulmonary circulation were not found in more than about a third of these patients either at rest or during exercise. The pathogenesis of dyspnoea in AS is not clear, as in many other conditions.

Chest pain on effort was the next most common symptom, with a duration that was sometimes just as long as for dyspnoea. The prognosis is, however, more serious after the onset of this symptom than after the onset of dyspnoea. Chest pain on effort was, compared with dyspnoea, uncommon in mild stenosis but also less common in pronounced stenosis. As the only symptom, it is seen especially in younger patients. The author's own findings in a series of post-mortem cases support information from the literature that the cause of chest pain on effort, which in about two-thirds of the patients in this series fulfilled the criteria of angina pectoris, is only exceptionally coronary sclerosis, in spite of the presence of often pronounced myocardial fibrosis.

Dizziness and syncope on effort occurred practically exclusively in AS. These symptoms did not occur in patients with a low gradient, but were just as common as chest pain on effort in those with high pressure gradients. The duration was shorter than for the symptoms mentioned above, and seldom exceeded 4 years. Neither in patients with this symptom nor in those with chest pain are there any characteristic findings, with regard to pressure or flow, on right heart catheterization. The pathogenesis is unknown. Opposing the view of a low cerebral blood flow is the fact that both in my own material and in others a normal cardiac output was usually found. The importance of arrhythmia is not clear. In a few cases a

normal ECG has been reported at the onset of syncope. Another hypothesis, finally, is that of peripheral vasodilatation.

Symptoms of left ventricular failure were seen in about 10% of the patients with AS and in 25% of those with ASAI. The duration of these symptoms was as a rule 6 months–1 year. They were only observed in pronounced AS or ASAI, with one exception where a myocardial factor was probably significant. Even in some patients with these symptoms, normal pressures and flow were found on right heart catheterization. In the few cases who performed a work test during the catheterization, a pathological rise in pressure was observed.

The majority of cases with aortic stenosis die in incompensation. Of these patients, who are usually completely disabled, some die in circulatory arrest, with no clinical signs of pulmonary stasis at death. Sudden death, completely unexpected in a patient with no or only few mild symptoms, seems on the other hand to be uncommon in AS. One case of this type, in whom ECG showed no S-T/T changes, is reported.

Objective signs

Several of the physical signs in aortic stenosis have been described since an early date. This is true of the small peripheral pulse (Riverius 1646, cit. Willius & Dry 1948), the palpatory signs of left ventricular hypertrophy (Corvisart 1812), the systolic murmur and thrill (Laennec 1823) and the attenuated second sound (Williams 1841).

According to McGinn & White (1934) and Kumpe & Bean (1948) the diagnosis of aortic stenosis was made far too often up to the time of the first World War, when it was found that many cases with purely functional heart symptoms of the Da Costa type also had a basal systolic murmur, which had previously resulted in the diagnosis of aortic stenosis.

By increasing the diagnostic criteria so as to comprise a basal systolic murmur with thrill, an inaudible or greatly attenuated second heart sound, a pathological peripheral pulse and a basal diastolic murmur (Lewis 1934, Brown 1939), aortic stenosis as a diagnosis became uncommon, and the previous over-diagnosis was superseded by under-diagnosis. This is shown, inter alia, by the fact that aortic stenosis had been diagnosed clinically in only 1/6–1/3 of the cases in autopsy series (Margolies, Ziellessen & Barnes 1931, McGinn & White 1934, Kumpe & Bean 1948). In a later study it was found that with the criteria mentioned above only 17% of cases with aortic stenosis verified at autopsy could be diagnosed clinically (Olesen & Warburg 1958).

Christian (1931 b) stressed once more that AS is not uncommon and can be diagnosed clinically. The most important criterion is a harsh, basal systolic murmur which should always lead to suspicion of aortic stenosis (McGinn & White 1934). In later series where the diagnosis has been verified at autopsy, the number of cases with a correct clinical diagnosis has been considerably higher (Andersson *et al.* 1952, Bergeron *et al.* 1954, Olesen & Warburg 1958).

Methods

The physical examination was performed in the usual way, as a rule by the author. Phonocardiograms (PCG) were recorded by means of a four-channel direct-writing ECG apparatus with a phonopreamplifier. The recordings were made after normal expiration, over the second right and left intercostal spaces, over the left sternal border in the fourth

intercostal space and over the apex, and sometimes also over further points of the precordium. For the recordings low frequency filters with nominal frequencies of 25 c/s, 100 c/s and one with "auditory" amplification were used (Kjellberg *et al.* 1959). The paper speed was 100 mm/sec.

Palpatory left ventricular hypertrophy, definite: when the ictus is palpated at least 2 fingers wide and heaving; suspected: when the ictus is increased in breadth but not heaving with certainty, and also when there is more diffuse pulsation over the apex.

Attenuated or inaudible *aortic component of the second heart sound.* The quality of the second sound was not noted on auscultation in three of the earlier cases. In these cases only the presence of an aortic component of the second heart sound on the PCG was noted. The results on this point must therefore be evaluated with reservation with regard to the sources of error which may arise.

The occurrence of a *fourth heart sound* on the PCG.

The *intensity of the basal systolic murmur* on auscultation, graded from 1–6 (Freeman & Levine 1933, Levine & Harvey 1959). In a few of the earlier cases this gradation was not applied. In these cases grade 4 was used where a thrill was noted, and in other cases grade 3.

The position in systole of the *maximal amplitude* of the murmur, the length of systole being calculated from the beginning of the first sound to the beginning of the second. The *duration* of the systolic murmur has been similarly expressed in relation to the length of systole on the PCG.

Of the other physical findings, the occurrence of a basal diastolic murmur, indicating AI, will be discussed later (chapter 6). The occurrence of an early systolic ejection sound (Lian & Welti 1937, Leatham & Vogelpoel 1954) will not be reported here. According to some authors the presence of this sign does not appear to have any correlation to the degree of severity of the stenosis (Wood 1958, Jones, Walker, Jahnke & Winn 1963, Braunwald *et al.* 1963), and this has also been corroborated by my own findings. The peripheral pulse signs will not be discussed here.

Results and discussion (*Table 19*)

In the AS group definite signs of *left ventricular hypertrophy* (LVH) were found in 10 out of 14 cases with a high gradient, and in 2 out of 12 with a low gradient. Definite LVH occurred in a higher frequency in the AS patients with a gradient of at least 25 mm Hg, than in those with a lower gradient (*). In group ASAI all patients with a low gradient had signs of hypertrophy, and 11 out of 15 with a high gradient.

Thus signs of LVH are not common in AS cases with a low pressure gradient, but are practically the rule in those with a high gradient. On the other hand, palpatory signs of LVH may be found in mild AS (Braunwald *et al.* 1963, Jones *et al.* 1963), and may be lacking in severe AS (Osler & Gibson 1915). It was considered previously that in children with AS palpatory LVH was uncommon (Kiloh 1950, Marquis & Logan 1955). In later studies, however, when the pressure gradient has been measured, this sign has been found in a high frequency (Braunwald *et al.* 1963).

In ASAI, where as a rule left ventricular dilatation also occurs, signs of LVH are found in a large percentage regardless of

TABLE 19. *Physical findings in AS and ASAI.*

Sign		AS PSG, mm Hg 0–24	AS PSG, mm Hg 25–74	AS PSG, mm Hg 75–133	ASAI PSG, mm Hg 0–49	ASAI PSG, mm Hg 50–152
LVH	+	2	8	10	9	11
	(+)	2	3	1	—	1
	0	8	6	3	—	3
A_2	– /0	—	5	9	2	13
	N/+	12	12	5	7	2
4th sound	+	1	4	3	1	4
	0	11	13	9	8	9
SM intensity	5–6	—	5	7	4	9
	4	4	9	6	4	4
	2–3	8	3	1	—	2
SM max	second half	—	7	6	4	10
	first half	11	10	7	5	2
SM duration	⩾ 80 %	2	11	12	7	11
	< 80 %	9	6	2	2	2

LVH = palpatory left ventricular hypertrophy. A_2 = aortic component of second heart sound. 4th sound = fourth heart sound. SM = systolic murmur over the aortic area. Max = maximal intensity. % = per cent of systole.

the pressure gradient. This is also in agreement with the findings of other authors (Osler & Gibson 1915, Matthews *et al.* 1955).

Palpatory signs of LVH may be found without organic causes, e.g. in hyperkinetic conditions (Gorlin *et al.* 1959). Falsely negative cases may partly be explained by rotation of the heart or by the sagittal diameter of the thorax.

An attenuated or absent aortic component of the second heart sound occurred in a higher frequency in AS cases with gradients of above 24 mm Hg than in those with lower gradients (*). Out of 31 patients with AS in whom there was a gradient of at least 25 mm Hg, 10 were over 50 years of age. In 9 of these 10 the second sound was attenuated, compared with 5 out of 21 cases below this age.

In group ASAI an attenuated sound occurred in a higher frequency among those with a gradient of more than 50 mm Hg than in those with a lower gradient (**). All cases with a gradient of below 50 mm Hg were less than 50 years old. Of those with a gradient of above 50 mm Hg, 13 were less than 50 years old, of whom 11 had an attenuated second sound.

In 35 patients out of 40 (AS + ASAI) above the age of 30 years, there were roentgenologically manifest calcifications in the aortic valve. The second sound was judged as normal in 9 of these 35 cases. All 5 patients without calcifications had a normal sound.

Both in children and adults with AS, a normal or accentuated second sound is not seldom found in spite of tight stenosis, and similarly in mild AS an attenuated or in-

audible second sound is not unusual (McGinn & White 1934, Bergeron *et al.* 1954, Matthews *et al.* 1955, Aravanis & Luisada 1957, Bouvrain & Vasselin 1958). In particular a normal second sound appears to be common in congenital AS (Grishman *et al.* 1947, Marquis & Logan 1955, Reinhold, Rudhe & Bonham-Carter 1955, Nadas 1957, Kjellberg *et al.* 1959). In other series, however, an attenuated second sound has been reported in 30–50% (Campbell & Kauntze 1953, Downing 1956, Ongley *et al.* 1958, Beuren *et al.* 1961 b). In series consisting mainly of adult patients an attenuated second sound has been found in 40–60% (Bergeron *et al.* 1954, Matthews *et al.* 1955, Olesen & Warburg 1958, Bouvrain & Vasselin 1958, Baker & Somerville 1959). The second sound may be normal even in patients with a calcified aortic valve (Kiloh 1950, Matthews *et al.* 1955, Bouvrain & Vasselin 1958).

A reversed or paradoxical splitting of the second heart sound (Leatham 1958) was not found on auscultation in the present material. Braunwald *et al.* (1963), by means of PCG, recorded the position of the two sound components during both inspiratory and expiratory apnoea. A reversed splitting was found in only 4 out of 45 cases with a gradient of above 70 mm Hg.

A *fourth heart sound* on PCG was unusual in this material, and showed no relationship either to age or pressure gradient. A fourth heart sound may occur normally in children. In adults it is found especially in hypertension and myocardial infarction, and is considered to be due to decreased distensibility of the myocardium (Weitzman 1955, Leatham 1958). It was considered previously to be rare in aortic stenosis (Weitzman 1955, Leatham 1958). Recently, however, some correlation between the occurrence of a fourth sound and the pressure gradient has been found in congenital AS (Goldblatt, Aygen & Braunwald 1962, Braunwald *et al.* 1963).

A *basal systolic murmur* was heard in all cases. In no case was the murmur louder over the apex than over the base, but in some cases it was of the same intensity at both sites. As may be seen in Table 19, in AS a murmur of grade 4–6 occurred in a higher frequency with gradients of at least 25 mm Hg than with lower gradients (**), and also with gradients of 25–74 mm Hg compared with lower gradients (*). The only patient with a high gradient and a murmur of grade 2–3 had no signs of failure. The majority of the ASAI patients had a murmur of at least grade 4.

No constant relationship between the intensity of the murmur and the degree of severity of the stenosis has been found in previous studies (Lewis 1934, Mitchell *et al.* 1954, Marquis & Logan 1955, Nadas 1957, Levine & Harvey 1959, Baker & Somerville 1959, Jones *et al.* 1963). Such a corleration has been reported, however (Kumpe and Bean 1948, Kjellberg *et al.* 1955). In the author's material, too, a loud murmur was found especially in cases with moderate-severe stenosis, while a faint murmur could be found in all grades of stenosis (cf. Bergeron *et al.* 1954, Normand 1957, Bouvrain & Vasselin 1958).

Since the intensity of the murmur depends not only on the degree of stenosis but also on other factors, such as the size of the stroke volume, some lack in agreement between the degree of stenosis and the intensity of the murmur is to be expected. In patients with a low flow rate, such as in concomitant mitral stenosis or incom-

pensation, the murmur may become fainter (Christian 1931 b, Matthews *et al.* 1955), but probably never disappears (Levine & Harvey 1959). For the same reason very loud systolic murmurs may be found in cases with an increased total stroke volume, such as in ASAI, even when the AS is mild (Corrigan 1832, Leatham 1958, Wood 1958). Systolic ejection murmurs may be found in dilatation of the ascending aorta (Chisholm 1937, Leatham 1958).

In all cases except one (case 33) the murmur was transmitted to the neck, where it was louder on the left side in 18 cases, and on the right in 3 cases. In 8 cases there was no difference between the two sides, and in the remaining cases no note was made in this respect. This finding has been discussed in a preliminary communication (Ask-Upmark & Cullhed 1963). Since the differences were never great, these observations must be assessed with some caution. It has been reported previously that the murmur is loudest on the right side (Cohen, Gray, Nash & Fink 1940, Ongley, Sprague, Rappaport & Nadas 1960).

In 5 cases the murmur was louder over the neck than over the base, which may be due to the position of the orifice in relation to the anterior chest wall. This finding is not entirely uncommon (Levine & Harvey 1959) and need not mean that the murmur is caused by pathological changes in the cervical vessels (cf. Dittrich 1961).

The *maximal intensity of the systolic murmur.* In aortic stenosis the murmur has the diamond shape characteristic of a systolic ejection sound (Lian & Racine 1933, Leatham 1951, 1958). The position of the maximal intensity of the murmur in systole can thus be determined in most cases by PCG. It was then found (see Table 19) that in all cases of AS with a low gradient the murmur reached its maximum within the first half of systole, while in 50% of the cases with a moderate or high pressure gradient a maximum was found in the latter half of systole. In the ASAI group a maximum in late systole occurred in 50% of the cases with a low gradient and in the majority of those with a high gradient.

A relationship between the degree of stenosis and the position in systole of the maximal intensity of the murmur has been found by some authors (Kjellberg *et al.* 1955, Aravanis & Luisada 1957, Daoud, Reppert & Butterworth 1959, Braunwald *et al.* 1963), but in other studies this has not been confirmed (Nadas 1957, Ongley *et al.* 1958).

The *duration of the murmur.* In group AS a duration of at least 80% of systole occurred in a higher frequency among cases with a gradient of at least 25 mm Hg than in those with a lower gradient (**). In group ASAI a long duration was found as a rule, regardless of the pressure gradient.

As in the case of the maximal intensity, some authors have found no correlation between the degree of severity of the stenosis and the duration of the murmur (Nadas 1957, Ongley *et al.* 1958), while in other studies such a correlation has been claimed (Kjellberg *et al.* 1955, Leatham 1958), at least in the absence of concomitant AI (Wood 1958). Prolongation of the systolic ejection phase has been described in patients with AS (Katz & Feil 1925, Katz, Ralli & Sheer 1928, Fleming & Gibson 1957, Epstein & Coulshed 1964).

When the occurrence of a pathological finding for each of the six criteria given in Table 19 was given 1 point, it was found that the mean number of points for the AS

patients with a low pressure gradient was 1.25 (S.E. 0.22), for those with a moderate gradient 3.06 (S.E. 0.35) and for those with a high gradient 4.00 (S.E. 0.26). The difference between the means for the patients with low and moderate pressure gradients was significant (***), as also was the difference between those with moderate and high gradients (*). In group ASAI, on the other hand, no significant difference was obtained between the mean values (3.75 and 4.21 points) for the two sub-groups.

Conclusions

In group AS palpatory left ventricular hypertrophy occurred in isolated cases with a low pressure gradient, and was sometimes absent in spite of a high gradient. In group ASAI this sign was found in the majority of cases, regardless of the size of the gradient.

The aortic component of the second heart sound was in the AS group normal in all cases with a low gradient, and attenuated or absent in a higher frequency among those with higher gradients. In the ASAI group the second sound was attenuated considerably more often in patients with a high gradient. This finding was more common in older patients. The sound was normal in cases without roentgenologically manifest valvular calcifications, as well as in a fourth of the patients in whom calcifications were observed. A pathological second sound indicates a moderate or tight stenosis, but a normal sound does not prove that the stenosis is mild. A fourth sound was heard in only a few cases.

Even though a loud basal systolic murmur was more common in the groups with high pressure gradients, a murmur of grade 4 was found in some cases with low gradients, and a murmur of grade 2–3 in some cases with moderate-high gradients. In group ASAI the majority had a loud murmur regardless of the size of the gradient. The systolic murmur was transmitted to the neck, as a rule somewhat louder on the left side.

In AS with a low pressure gradient the maximal intensity always occurred in the first half of systole. A maximum occurring late in systole was equally common in the patients with moderate and high pressure gradients, both in the AS and the ASAI groups. In group AS the duration of the murmur was shorter in the patients with a low pressure gradient than in those with moderate or high gradients. The murmur in ASAI was usually of long duration regardless of the size of the gradient.

To summarize, it is found that in patients with AS the physical signs, and the phonocardiogram, are of more value for separating the group with a low pressure gradient from groups with higher gradients than for distinguishing between the groups with moderate and high gradients. However, most signs occurred in higher frequency at higher pressure gradients. In group ASAI only one sign was found which more markedly distinguished the patients with low from those with high pressure gradients, namely the quality of the second heart sound.

Indirect systemic arterial pressure

It has earlier been considered that in aortic valvular diseases the characteristic features of the peripheral blood pressure are a small pulse pressure in AS and a large

TABLE 20. *The indirect brachial arterial pressure (mm Hg) in relation to the objective classification.*

		AS PSG, mm Hg			ASAI			
					Degree AS PSG, mm Hg		Degree AI	
		0–24	25–74	75–133	0–49	50–152	AI:3	AI:4
	n	12	17	14	9	15	9	15
Syst.	M	118.8	125.3	122.5	138.9	133.3	141.1	132.0
	S.E.	5.30	4.06	2.76	10.70	4.82	6.33	6.88
	S.D.	18.36	16.73	10.34	32.09	18.68	19.00	26.65
Diast.	M	79.2	85.3	82.5	75.0	72.7	88.3[a]	64.7[a]
	S.E.	3.19	3.36	3.31	5.27	4.73	4.57	3.14
	S.D.	11.05	13.86	12.37	15.81	18.30	13.71	12.17
Pulse press.	M	39.6	40.0	40.0	63.9	60.7	52.8	67.3
	S.E.	3.62	3.13	4.48	11.21	5.09	4.50	7.53
	S.D.	12.53	12.88	16.76	33.62	19.72	13.49	29.16

[a] The difference between these means is significant (***). The differences between other means within group AS and within group ASAI are not significant.

pulse pressure in AI. Among other criteria the size of the pulse pressure has been used to distinguish, among patients with ASAI, between those in whom the AS and those in whom the AI is predominant (e.g. Gorlin *et al.* 1955). It seemed therefore of interest to compare the blood pressure in groups with different degrees of AS and AI in this material.

The blood pressure was measured in the right arm with a mercury manometer, with the patient in the recumbent position. Recommended criteria for systolic and diastolic blood pressures were used (Bordley, Connor, Hamilton, Kerr & Wiggers 1951).

Results and discussion

The results are shown in Table 20. In group AS no significant differences were found between patients with low, moderate and high pressure gradients, either for the systolic, diastolic or pulse pressure. Isolated cases with a pulse pressure of below 30 mm Hg or above 50 mm Hg were found in all three sub-groups. Neither were any significant differences found in group ASAI between the patients with low and those with high pressure gradients. It was found, on the other hand, that in the patients with the most pronounced AI the diastolic pressure was lower and the pulse pressure higher, although the difference in pulse pressure was not significant. Neither in the AS or the ASAI groups were higher pressures found in the patients of function class III + IV. A comparison between groups AS and ASAI (Table 21) showed higher mean values in the latter group for the systolic and pulse pressures, and lower for the diastolic pressure. The difference was most pronounced for the pulse pressure.

No case of hypertension was found. It

TABLE 21. *The indirect brachial arterial pressure (mm Hg) in groups AS and ASAI.*

		AS	ASAI	Diff.
	n	43	24	
Syst.	M	122.6	135.4	+12.8*
	S.E.	2.34	4.91	5.44
	S.D.	15.33	24.04	
Diast.	M	82.7	73.5	−9.2*
	S.E.	1.92	3.49	3.99
	S.D.	12.61	17.09	
Pulse	M	39.9	61.9	+22.0***
press.	S.E.	2.11	5.13	5.55
	S.D.	13.82	25.14	

is true that in 12 cases diastolic pressures of 95–110 mm were noted, but on later direct measurement values of below 95 mm Hg were obtained. No consideration has been taken of the influence of age.

In some previous reports it has been stated that the pulse pressure in AS is low (Lewis 1934, Campbell & Kauntze 1953, Kjellberg *et al.* 1959). Most authors have found that in AS normal blood pressures are usually found, but that a low pulse pressure is more common in tight stenosis while high pulse pressures may be found in all grades of stenosis (McGinn & White 1934, Kumpe & Bean 1948, Mitchell *et al.* 1954, Keith *et al.* 1958, Wood 1958, Morrow *et al.* 1958, Baronofsky *et al.* 1959, Beuren *et al.* 1961 b). Gillmann & Loogen (1960) compared the mean systolic, diastolic and pulse pressures in groups with different pressure gradients. They found no differences in the diastolic pressures, while the systolic and pulse pressures fell with increasing gradients. The difference was greater between the groups with low and moderate gradients than between those with moderate and high gradients. In a similar comparison Hancock & Fleming (1960) found that one-third of both cases with pronounced and those with mild stenosis had a pulse pressure of below 35 mm Hg.

It thus appears that among patients with AS, whether the degree of severity is evaluated according to the peak systolic gradient or to the calculated aortic valve area (Hancock & Fleming 1960), no significant differences in blood pressure are found between those with mild, moderate and pronounced stenosis.

A difference in blood pressure was found, on the other hand, between groups with AS and those with ASAI. In spite of the fact that two-thirds of the latter group had pronounced AS, a raised pulse pressure was found, as in pure AI, due to increased stroke volume, backflow to the left ventricle and peripheral vasodilatation (Gorlin & Goodale 1956).

The peripheral vasoconstriction with rise in blood pressure associated with incompensation and reduced cardiac output, demonstrated by Sahli as early as in 1901, has also been described in aortic valvular diseases (Lang & Manswetowa 1908, Lewes 1951, Gorlin & Goodale 1956, Beuren *et al.* 1961 b). In this material no certain deviations in blood pressure were found in the few cases with a low flow rate.

No comparisons between the direct (Table 10) and indirect blood pressures (Ragan & Bordley 1941, Engstedt, Holmgren & Ström 1956, Berliner, Fujiy, Ho Lee, Yildiz & Garnier 1960) were made, since the blood pressures were not measured simultaneously or in the same arteries.

Conclusions

In patients with aortic stenosis no differences in the indirect arterial pressure

were found between groups with different pressure gradients. On the other hand higher pulse pressures were found on an average in group ASAI than in group AS, and in the former group lower diastolic pressures in patients with the most pronounced AI. Because of the wide range, however, the pulse pressure is of limited value in determining in the individual case whether, apart from AS, a significant degree of AI is also present.

Electrocardiogram

A high frequency of ECG changes have long been noted in aortic stenosis (Willius 1927, Dry & Willius 1939 b). In the following the relationship between the occurrence of signs of left ventricular hypertrophy (LVH) and the systolic pressure gradient will be discussed. A similar comparison between the ECG and the angiographic thickness of the left ventricular wall will be discussed in chapter 6.

Methods

The ECG was recorded by means of a four-channel direct-writing apparatus (Mingograf 42, Elema). The criteria of LVH used here agreed with those established by Sokolow & Lyon (1949). The criterion of high voltage, however, was placed at a somewhat higher value, in consideration of the risk of falsely positive diagnoses in younger persons (Nadas 1957, New York Heart Association 1964).

The following ECG criteria were used:

High voltage = the sum of S in V_1 and R in V_5 or V_6 is at least 4 mV.

Prolonged left ventricular activation time (*VAT*): when this is at least 0.06 sec. in V_5 or V_6.

Negative T waves over the left precordium: biphasic or negative T waves in V_5 or V_6, combined with a depressed S-T segment.

The voltage was calculated from the upper margin of the isoelectric line to the tip of the R wave, and from the lower margin to the tip of the S wave, respectively. Since only the alternative above or below 4 mV was noted, no consideration was taken of the non-linear distortion of the apparatus. The VAT was measured from the beginning of the QRS complex to the peak of the R wave, with the aid of a magnifying glass. One case of right bundle branch block was excluded. In 6 cases the S-T/T changes were considered to be due to digitalis, and these cases were therefore excluded. In 8 cases the T waves were judged to be an expression of LVH despite concomitant digitalis therapy. In these cases the negative T wave was preceded by a depressed S-T segment with an upwardly convex form—"left ventricular strain". Since, however, assessment of S-T and T changes is always uncertain during digitalis therapy, these cases have been reported separately in the table.

Results (*Table 22*)

It was found that in the AS group high voltage occurred as the only positive criterion in 4 cases of those with the lowest gradient, of whom 3 were below 15 years of age. This sign was found in about 70 % of the patients with moderate and high pressure gradients, and in one-third of these patients this was the only sign of LVH. There were no significant differences between the different groups.—In ASAI groups with different pressure gradients and

TABLE 22. *The electrocardiographic diagnosis of left ventricular hypertrophy in relation to the objective classification.*

ECG in left precordial leads		AS PSG, mm Hg			ASAI PSG, mm Hg			
					0–49		50–152	
		0–24	25–74	75–133	AI:3	AI:4	AI:3	AI:4
$S_{V_1} + R_{V_5\,V_6} \geq 4$ mV	Total	4	13	9	2	6	4	8
	Sole	4	5	3	1	—	—	—
VAT ≥ 0.06 sec	Total	—	4	3	1	6	2	5
	Sole	—	—	—	—	—	—	—
Neg. T	Total	—	7(1)	6(1)	—	5(1)	4(2)	9(3)
	Sole	—	1	1	—	—	1	1(1)
Prolonged VAT and/or neg. T		—	10	7	1	6	4	9
No positive criterion		8	3	4	1	—	—	—
Total No. of cases		12	17	14	3	6	6	9

The figures in brackets denote cases with the "strain type" of negative T waves, but who were taking digitalis.

degrees of AI there was a high frequency of this criterion, but it was always found, however, together with other criteria of LVH.

Prolonged VAT did not occur in the AS cases with a low gradient, but was found in approximately the same frequency in those with moderate and high gradients. This criterion was found in a higher frequency in ASAI than in AS, especially among the patients with AI of grade 4.

As in the case of prolonged VAT, negative T waves did not occur in AS with a low gradient, and was found in just under half of the cases with moderate and high gradients, usually not as the only criterion of LVH. Negative T waves occurred in 6 out of 9 cases with AS and a pressure gradient of at least 100 mm Hg, and prolonged VAT was recorded in only 2 of these 6. In group ASAI negative T waves were noted in the majority with a pressure gradient of above 50 mm Hg or grade 4 AI. In all 6 ASAI cases with a gradient of at least 100 mm Hg pathological T waves were seen.

An ECG without any of these signs of LVH was recorded even in cases with a high pressure gradient in the AS group, but only in one case with ASAI. Other criteria of LVH have not been reported since they did not appear to have any relationship to the pressure gradient. Signs of cardiac infarction were not found. Atrial fibrillation was noted in 2 cases with AS and 2 with ASAI. All of these had considerable heart enlargement; in two of them there was pronounced stenosis with a high gradient. In one case there was negligible stenosis, and atrial fibrillation began in association with myocarditis (case 33, appendix 2). The fourth case (case 120, appendix 2) had pronounced myocardial disease and mild mitral stenosis.

A comparison between patients with and

without chest pain on effort with regard to the occurrence of negative T waves showed that these were recorded in 20 out of 27 cases with this symptom, but only in 11 out of 34 cases without chest pain on effort. This difference is significant (**).

On comparing groups AS and ASAI it was found that all the criteria of LVH used here occurred in a higher frequency in the latter group. The level of significance for the difference between the two groups was lower for high voltage (*) than for negative T waves (***) and prolonged VAT (***).

Discussion

Comparisons between the ECG signs of LVH and autopsy findings have shown that LVH may be found at autopsy in cases where the ECG was normal, and also the reverse. Thus the ECG diagnosis, in relation to the anatomical findings, may be both falsely positive and falsely negative (Scott 1960, Selzer, York, Naruse & Pierce 1960, Allenstein & Mori 1960, Rosenfeld, Goodrich, Kassebaum, Winston & Reader 1962). The diagnosis of LVH at autopsy may also be erroneous, whether it is based on increased weight (subepicardial fat) or increased wall thickness (rigor mortis, oblique section, etc.).

In earlier studies, before methods of pressure measurement in the left ventricle were available, it was reported that ECG signs of LVH always indicated and were always found in moderate-severe stenosis (Marquis & Logan 1955, Ongley *et al.* 1958, Morrow *et al.* 1958, Wood 1958). In exceptional cases, however, a normal ECG may be found in spite of pronounced stenosis (Dry & Willius 1939 b, Matthews *et al.* 1955, Snellen *et al.* 1961). A comparison between the frequency of negative T waves over the left precordium in AS, hypertension and coarctation of the aorta, with corresponding degrees of LVH, assessed at autopsy or according to the degree of high voltage, showed that this frequency was considerably higher in AS (Abdin 1958). This may agree with the concept of relative coronary insufficiency in valvular AS (see page 61). In some series of AS with a longer follow-up period, the mean survival time was found to be longer in cases with positive T waves in lead I than in those with isoelectric or negative T waves (Aastrup & Petersen 1952, Olesen & Warburg 1958).

In some investigations in recent years the ECG has been correlated to the systolic pressure gradient. Fleming & Gibson (1957) found negative T waves in all cases with a gradient of above 60 mm Hg, and in 21 out of 22 cases with a gradient of at least 40 mm Hg. In a small series Dexter *et al.* (1958) found a case with a normal ECG despite a high gradient. Abelman & Ellis (1959) found ECG signs of LVH equally often in pronounced as in mild stenosis. They did not state their ECG criteria, however, nor the age distribution or incidence of coronary sclerosis in the two groups.

In agreement with the findings in the present investigation, Braunwald *et al.* (1963) reported poor correlation between the occurrence of high voltage and the pressure gradient in adults. They found better correlation in cases below 10 years old. In the present study, as in others, it was found that even with high pressure gradients normal T waves over the left precordium were not unusual (Hancock & Fleming 1960, Hugenholtz, Lees & Nadas 1962, Braunwald *et al.* 1963, Jones *et al.* 1963). The question of whether sudden death can occur

in spite of a previously normal ECG has been discussed (Marquis and Logan 1955, Reynolds, Nadas, Rudolph & Gross 1960).

It was considered earlier that the ECG picture was the same in AS as in ASAI (Matthews *et al.* 1955, Wood 1958), but the findings in the present study, as in others, show that ECG signs of LVH are considerably more common in ASAI (Kjellberg *et al.* 1959, Hancock & Fleming 1960).

Conclusions

In the AS group high voltage occurred in one-third of the cases with a low gradient and in two-thirds of those with moderate or high gradients. Prolonged left ventricular activation time and negative T waves over the left precordium did not occur in AS patients with a low pressure gradient, but were found in approximately the same frequency in cases with moderate as in those with high gradients. Thus in AS pronounced ECG changes indicate a moderate or high pressure gradient, while the absence of signs of LVH does not preclude a high pressure gradient. Negative T waves occurred more often in patients with chest pain provoked by effort.

All the ECG signs of left ventricular hypertrophy used here were considerably more common in the ASAI group. In this group negative T waves occurred in all cases with a high pressure gradient or with pronounced AI.

Chest roentgenogram

A chest radiogram was made routinely in all cases. The films in the frontal and lateral projection, and also the tomograms, were studied. This study comprised evaluation of the pulmonary vessels and heart configuration, calculation of the heart volume and examination for the presence of calcifications. Signs of aortic dilatation are discussed in chapter 6.

The heart configuration

Evaluation of the size of the individual heart chambers on conventional chest radiograms should always be made with caution, since the risk of falsely positive diagnoses is large. A heart chamber may appear to be enlarged due to its dislocation by another chamber, and rotation of the heart often adds to this effect (Kienböck 1918, Dressler 1940). In pronounced heart enlargement the individual chambers often cannot be evaluated with certainty. These difficulties have long been known, not least with regard to the evaluation of the left ventricle (Lehman & Curry 1954, Jönsson 1957, Amplatz 1962, Zdansky 1962). When therefore in the following enlargement of a certain heart chamber is discussed, this only means that certain given criteria have been fulfilled.

Such an evaluation has nevertheless been considered motivated, since similar assessments are common in studies of aortic valvular disease, and since they often constitute the only attempt at quantitative evaluation of the size of the heart.

Pulmonary vessels. No calibre changes in the pulmonary arteries or veins were found, nor Kerley's B-lines. These changes are seen in particular in mitral stenosis, but have also been described in left ventricular failure (Grainger & Hearn 1955/56, Short 1956, Steiner 1959/60). Other authors have also found, however, that these signs are uncommon in aortic stenosis (Baker & Somerville 1959), which is probably associated with

the shorter duration and lower degree of pulmonary hypertension in this condition compared with the mitral valvular diseases.

Right ventricle and left atrium. The right ventricle was considered to be enlarged when the heart tended to obliterate the retrosternal space in the lateral projection (Jacobsson, Poppel, Hanenson & Dewing 1952). The left atrium was regarded as enlarged when an increased bulge dorsal to the position of the atrium was seen (Jacobson *et al.* 1952). No other signs of enlargement of the left atrium were observed in this material.

Enlargement of the right ventricle was noted in 4 cases, in 2 of whom the left atrium was also enlarged. A further 2 cases had enlargement of the left atrium. All of these 6 cases had a raised pulmonary artery mean pressure at rest (mean 45 mm Hg, range 28–65 mm Hg), and heart enlargement (660–1070 ml/m^2). The pulmonary artery mean pressure was also raised in a further 6 cases (mean 35 mm Hg, range 27–50 mm Hg). Heart enlargement occurred in 4 of these cases (610–760 ml/m^2).

It has been found in previous studies that enlargement of the right ventricle or left atrium in AS indicates that the stenosis is severe (Marquis & Logan 1955, Braunwald *et al.* 1963), and that these findings are seen in cases with a history or haemodynamic signs of left ventricular failure (Downing 1956, Baker & Somerville 1959, Rockoff & Austen 1963, Lehman, Florence, Schimert & Evans 1963). Both these observations and the author's own findings show that enlargement of the left atrium or right ventricle in AS indicates pulmonary hypertension, while the absence of these signs does not mean that this condition is not present.

Left ventricle. Two of the criteria used (Table 23) are based on the observation that on enlargement the left ventricle expands dorsally (Dressler 1940, Parkinson 1949), whereby an increased bulge caudal to the left atrium or a bulge dorsal to the oesophagus is seen in the lateral projection (Jacobsson *et al.* 1952, Lehman & Curry 1954, McKay & Aitchison 1954/55). Further, a criterion which has long been used, i.e. increased bulging of the left heart contour in the frontal projection, was evaluated. This sign, and to a certain extent that mentioned first above, are based on subjective evaluation, while the occurrence of the second criterion, a bulge dorsal to the oesophagus, is easily determined.

The *results* are shown in Table 23. At least one sign of left ventricular enlargement was positive in 65 % in the AS group and in 60 % in group ASAI. No significant difference in the occurrence of signs of left ventricular enlargement was found in the groups with different pressure gradients. The absence of these signs ("No LVE", Table 23) was, however, in several cases due to the aforementioned difficulty in the evaluation of large hearts. A higher frequency of heart enlargement was found in cases where roentgen sign A (**) according to the table, or roentgen sign C (***) was positive, than in those without these signs. Criterion B was less sensitive but possibly more specific.

In previous studies left ventricular enlargement has been stated to occur in between 50 % and 100 % of cases with AS. The criterion of this condition has been increased rounding of the left heart contour in the frontal projection, probably also in the studies where the criterion has not been stated (Scherf & Boyd 1943, Kiloh 1950, Lewes 1951, Downing 1956, Olesen & War-

TABLE 23. *The roentgenological diagnosis of left ventricular enlargement (LVE).*

Roentgen LVE	AS PSG, mm Hg				ASAI				
					AS PSG, mm Hg		AI		
	0–24	25–74	75–133	Total	0–49	50–152	AI : 3	AI : 4	Total
A	4(2)	8(3)	7(6)	19(11)	7(5)	10(9)	7(5)	10(9)	17(14)
B	—	3(0)	4(3)	7(3)	1(0)	5(5)	2(2)	4(3)	6(5)
C	3(2)	9(5)	6(5)	18(12)	8(6)	10(9)	7(5)	11(10)	18(15)
No LVE	7(0)	4(0)	4(1)	15(1)	—	5(4)	1(1)	4(3)	5(4)
Total No.	12(2)	17(5)	14(7)	43(14)	9(6)	15(13)	9(6)	15(13)	24(19)

A: The left ventricle extends caudal to the left atrium in the lateral view. *B:* The left ventricle extends dorsal to the oesophagus in the lateral view. *C:* A globular rounding of the left heart contour in the frontal view.

No LVE: none of the criteria *A*, *B* or *C* were positive. The first figure denotes the total number of cases fulfilling the criteria *A*, *B* or *C*; the figure within brackets denotes the number of cases with increased heart volume.

burg 1958, Ongley *et al.* 1958, Kjellberg *et al.* 1959, Baker & Somerville 1959). Marquis & Logan (1955) and Matthews *et al.* (1955), on the other hand, claim that enlargement of the left ventricle (their criteria are not defined) is uncommon in AS and indicates incompensation or concomitant AI. The same criteria in principal as those in the present investigation were used by Amplatz (1962) who considered that signs of left ventricular enlargement are not seen until the ventricle is dilated, since they can be completely absent in pronounced stenosis.

In recent studies, where the degree of stenosis has been determined with the aid of the pressure gradient, left ventricular enlargement has been found to be common but to have no correlation to the size of the gradient (Dexter *et al.* 1958, Klatte, Tampas, Campbell & Lurie 1962, Gorman, Calatayud, Cronin, Reid & Scott 1962, Rockoff & Austen 1963, Lehman *et al.* 1963, Braunwald *et al.* 1963). The criterion used in these investigations was an evaluation of the left heart contour in the frontal projection. Klatte *et al.* (1962) considered that a rounded left contour indicated concentric hypertrophy and was common in AS, while enlargement dorso-caudally in the lateral projection indicated coincident dilatation.

Heart volume

This was calculated according to the method of Jonsell (1939). Normal values have been given, inter alia, by Jonsell (1939) and Maurea, Nylin & Sollberger (1955). In healthy persons, the volume seldom exceeds 500 ml/m^2 body surface area for men and 450 ml/m^2 for women. All pictures were taken with the patient in the sitting position.

The *results* are given in Table 24. In group AS heart enlargement occurred in 33% and in group ASAI in 79%. Only 3 cases out of 43 with AS had a heart volume exceeding 700 ml/m^2, compared with 13 out of 24 cases with ASAI. Aortography in

TABLE 24. *The roentgenological heart volume (ml/m²) in relation to the objective classification.*

	AS PSG, mm Hg			ASAI			
				AS PSG, mm Hg		AI	
	0–24	25–74	75–133	0–49	50–152	AI : 3	AI : 4
n	12	17	14	9	15	9	15
M	363	468	489	601	670	587	679
S.E.	41	29	40	52	46	50	45
S.D.	141	118	152	157	176	151	175

Only the difference between the means for the AS group with a low gradient (0–24 mm Hg) and that with a moderate gradient (25–74 mm Hg) is significant (*).

2 of the 3 cases with AS showed no AI and grade 2 AI, respectively. Larger heart volumes were found with higher gradients and with higher grades of AI, but the differences were usually not significant. This also held when the material was classified according to the degree of disability (Table 25). Heart enlargement was found in 8 out of 28 without disability and in 12 out of 14 with pronounced disability. Out of 16 cases with a pulmonary artery mean pressure at rest of over 20 mm Hg, 12 had heart enlargement. With regard to age, it was found that in the AS group heart enlargement occurred in 2 cases out of 27 below 40 years, compared with 12 cases out of 16 above this age. This difference was significant (***). In the ASAI group heart enlargement occurred in a high frequency in all ages.

In previous studies it was found, understandably, that in post-mortem series, where the roentgen picture had probably been taken on incompensated patients, heart enlargement was very common, assessed either according to criteria which were not stated (Kumpe & Bean 1948, Lewes 1951), or by measurement in the frontal plane (Olesen & Warburg 1958). In clinical studies, on the other hand, heart enlargement has been

TABLE 25. *The roentgenological heart volume (ml/m²) in relation to the degree of disability.*

	AS			ASAI		
	I	II	III + IV	I	II	III + IV
n	22	14	7	6	11	7
M	402	445	581	510	643	761
S.E.	28	38	33	52	39	70
S.D.	133	143	88	127	130	185

Only the difference between the means for group II and group III + IV with AS is significant (*).

TABLE 26. *The number of cases with roentgenologically demonstrated calcifications (numerator), and the total number of cases in each group (denominator), classified according to age and pressure gradient (AS + ASAI).*

Age, years	PSG, mm Hg		
	0–24	25–74	75–152
7–19	0/10	0/7	0/3
20–39	0/3	5/9	4/5
40–59	5/6	6/6	14/14
60–66	0/0	3/3	1/1

stated to be uncommon in AS without AI or signs of failure (Scherf & Boyd 1943, Marquis & Logan 1955, Downing 1956). Other investigators have reported cardiac enlargement in 24%–40% on measurement in the frontal plane alone (Campbell & Kauntze 1953, Keith *et al.* 1958, Baker & Somerville 1959). It was considered earlier that there was no correlation between increased heart size and increased age (Campbell & Kauntze 1953, Marquis & Logan 1955), but such a relationship has since been shown (Tryggeseth 1958, Bevegård 1962).

In series of cases in whom left heart catheterization has been performed, no correlation has been found with the pressure gradient (Dexter *et al.* 1958, Gillmann & Loogen 1960, Klatte *et al.* 1962, Lehman *et al.* 1963, Braunwald *et al.* 1963). However, in these studies the cardiac size was only evaluated in the frontal projection.

Tomographic findings

Calcifications at a position corresponding to that of the aortic orifice can be shown by tomography (Hohenner 1940, Davies & Steiner 1949). In this study simultaneous tomography was used (Linko & Sysimetsä 1958) in the true lateral projection (Björk & Lodin 1963). Tomography was performed on 9 out of 20 cases below, and on all patients above the age of 20 years, with the exception of one case (case 107). In this case such distinct calcifications were seen on conventional chest radiograms that they were regarded as definitely positive.

The *results* are shown in Table 26. There was no difference in the frequency of calcifications between the groups with different pressure gradients. There was a higher frequency of calcifications in cases over 40 years than among younger cases (***). No calcifications were observed in patients under 20 years of age. In the age group 20–39 years calcifications occurred especially in those with high pressure gradients. Calcifications were found in the majority of patients above 39 years of age, regardless of the size of the gradient.

In 29 cases out of 37 with tomographically demonstrated calcifications, these were noted on conventional chest radiograms. Out of a total of 38 patients in whom calcifications had been shown roentgenologically, open operation or autopsy was performed on 19, at which calcifications were found in all of them. In 3 out of 6 cases without roentgenologically manifest calcifications small calcifications were found at operation or autopsy. In one 14-year-old girl (case 6) minute calcium deposits were felt at commissurotomy.

Valvular calcifications have been shown roentgenologically in aortic stenosis since an early date (Christian 1931 a, Sosman & Wosika 1933, Parade & Kuhlman 1933). Even though the opposite has been claimed (Dry & Willius 1939 a), the majority of authors consider that there is no correlation between the occurrence of calcifications and the

degree of stenosis (Mitchell *et al.* 1954, Matthews *et al.* 1955, Rockoff & Austen 1963, Braunwald *et al.* 1963). It is well known that roentgenologically manifest calcifications are very common in AS patients over the age of 40 years (Campbell & Kauntze 1953, Wood 1958, Björk *et al.* 1961 b), and also that in exceptional cases they may occur before the age of 20 years (Campbell & Kauntze 1953, Braunwald *et al.* 1963). The youngest in this material was 26-years old.

The concept that roentgenologically manifest calcifications demonstrate the presence of aortic stenosis (Contratto & Levine 1937, Parkinson 1949, Tryggeseth 1958, Gelfand 1960, Lindgren & Olsson 1963) should perhaps be discussed, at least with regard to the higher age groups where calcifications in the mitral annulus and the aortic cusps are common (Ashworth 1946, Hultgren 1948, Pyke & Symons 1951). Calcifications in the aortic cusps may be found without stenosis (Hope 1833, Ashworth 1946, Karsner & Koletsky 1947, Bedford & Cairn 1960), even though there is probably some degree of reduced mobility, sufficient to cause a systolic murmur. In contrast to calcifications in the mitral annulus calcifications in the aortic annulus probably do not affect the valvular function (Korn, DeSanctis & Sell 1962).

Conclusions

Changes in the roentgenological appearance of the pulmonary vessels are very uncommon in AS, and were not observed in this material. Signs of enlargement of the left atrium or right ventricle may be seen in pulmonary hypertension, which can also be present, however, without such signs. Enlargement of the left ventricle is generally considered to be common in AS and to lack any correlation to the pressure gradient. In the author's own experience these signs may be absent in pronounced stenosis. The correlation with increased heart volume suggests that these signs are positive especially on dilatation of the left ventricle.

The relative heart volume was found to have a certain degree of relationship to the objective and subjective degree of severity, although the spread of values in each group was large. In this material heart enlargement was very common in ASAI and not uncommon in AS. In cases with AS it was found that an increased volume was more common in the higher age groups.

Calcifications at the position of the aortic valve, observed at tomography, are uncommon in patients under 20-years old, although they have been reported occasionally in such cases. In the age group 20–39 years calcifications occurred especially among patients with a high gradient, while in patients above the age of 40 years they were common regardless of the size of the gradient. The demonstration of calcifications in patients below 40 years of age and with symptoms of AS therefore probably supports the diagnosis. The absence of calcifications in patients above this age opposes the diagnosis of stenosis.

Regression analysis of the relationship between the pressure gradient and some clinical data

I. Cullhed & G. Eklund

Earlier in this chapter the correlation between different clinical data (variables) and the pressure gradient has been discussed. These variables, taken separately, did not

TABLE 27. *Coefficients of product-moment correlation, with significance asterisks as defined on page 126, between pressure gradient and 13 x-variables, defined on page 80.*

x-variable	Correlation coefficient TS	P
x_1	0.41	0.53*
x_2	−0.06	0.38
x_3	0.34	0.61**
x_4	0.18	0.53*
x_5	0.76***	0.29
x_6	0.54*	0.26
x_7	0.55*	0.30
x_8	0.30	0.05
x_9	0.51*	−0.12
x_{10}	0.46	−0.09
x_{11}	0.43	−0.00
x_{12}	0.54*	0.27
x_{13}	0.10	−0.00

TS = transseptal method, $n = 16$.
P = direct puncture method, $n = 22$.

show such good correlation with the pressure gradient that any single variable could replace the determination of this gradient. In order to investigate whether in the individual case the gradient could be predicted by a combination of several clinical data, a linear regression analysis was performed (cf. appendix 1). This study was limited to group AS.

A study was made of the relationship between the pressure gradient in mm Hg, as dependent variable, called y, and different independent variables, called x_1–x_{13}. The independent variables were denoted and quantified as follows:

x_1 is a variable for the degree of clinical disability,
$x_1 = 0$ for no disability (class I),
$x_1 = 1$ for slight disability (class II),
$x_1 = 2$ for pronounced disability (class III + IV).

x_2 is a variable for chest pain,
$x_2 = 1$ for the occurrence of chest pain on effort,
$x_2 = 0$ for no chest pain on effort.

x_3 is a variable for dizziness,
$x_3 = 1$ for the occurrence of dizziness on effort,
$x_3 = 0$ for no dizziness on effort.

x_4 is a variable for palpatory LVH,
$x_4 = 1$ for the occurrence of definite palpatory LVH,
$x_4 = 0$ for no definite palpatory LVH.

x_5 is a variable for the intensity of the basal systolic murmur, according to the definition on page 64.

x_6 is a variable for the position of the maximal intensity of the systolic murmur, expressed as a percentage of systole (page 64).

x_7 is a variable for the duration of the systolic murmur, expressed as a percentage of systole (page 64).

x_8 is a variable for the fourth heart sound,
$x_8 = 1$ for the occurrence of this sound,
$x_8 = 0$ for no occurrence of this sound.

x_9 is a variable for high voltage,
$x_9 = 1$ for the occurrence of high voltage (R in V_5 or $V_6 \geqslant 3.5$ mV),
$x_9 = 0$ for no high voltage.

x_{10} is another variable for high voltage,
$x_{10} = 1$ for the occurrence of high voltage (S in V_1 + R in V_5 or $V_6 \geqslant 4.5$ mV),
$x_{10} = 0$ for no high voltage.

x_{11} is a variable for prolonged left ventricular activation time (VAT),
$x_{11} = 1$ for the occurrence of prolonged VAT ($\geqslant 0.06$ sec),
$x_{11} = 0$ for no prolonged VAT.

x_{12} is a variable for negative T waves over the left precordium,
$x_{12} = 1$ for the occurrence of such waves,
$x_{12} = 0$ for no occurrence of such waves.

x_{13} is a variable for left ventricular enlargement on the chest radiogram (rounded left contour in frontal projection),
$x_{13} = 1$ for the occurrence of such enlargement,
$x_{13} = 0$ for no occurrence of such enlargement.

Results

Table 27 shows that there was a distinct correlation between several of the variables x_1–x_{13} and the pressure gradient. Variables showing a strong correlation with y, i.e. x_1, x_3, x_5, and x_{12} were selected. These were then subjected to detailed study by means of a multiple regression analysis whereby the relationship between the value for the pressure gradient and these four variables was estimated. The variables x_6 and x_7 showed a strong correlation with y, but were not included due to the strong correlation between x_5, x_6 and x_7.

A multiple regression analysis including 38 patients was performed and the expected value of the pressure gradient according to this analysis was compared with the observed value for each patient. A comparison between patients investigated by direct puncture (P) and those on whom the transseptal technique was used (TS), showed different deviations between observed and expected pressure gradient. The material was therefore divided into 22 puncture and 16 transseptal cases. Another study was then made of the relationship between 1) the pressure gradient and variable x_5, and 2) the pressure gradient and the variables x_1, x_3, x_5 and x_{12}. The following problems were treated:

1) Has variable x_5 a greater predictive value for the variations in pressure gradient in the TS material than in the P material?

By regression analysis the following straight lines were obtained for the relationship between expected pressure gradient and variable x_5:

For the TS material:

$y = -90 + 36.0 \cdot x_5$ (residual standard deviation 27.0).

For the P material:

$y = 16 + 11.25 \cdot x_5$ (residual standard deviation 40.7).

It was found that the regression coefficients 36.0 and 11.25 were significantly different (*), as also were the residual standard deviations 27.0 and 40.7 (*).

2) Has a suitable weighting of the variables x_1, x_3, x_5 and x_{12} a greater predictive value for the observed individual values of the pressure gradient in the TS material than in the P material?

The following equations were obtained by multiple regression analysis:

For the TS material:

$y = -83.8 + 31.9 \cdot x_5 + 8.8 \cdot x_1 + 57.3 \cdot x_{12} - 49.7 \cdot x_3$ (residual standard deviation 23.3).

For the P material:

$y = 14.9 + 4.0 \cdot x_5 + 17.0 \cdot x_1 + 8.2 \cdot x_{12} + 40.6 \cdot x_3$ (residual standard deviation 31.8).

The coefficients of variable x_5 (31.9 and 4.0) show considerable deviation, which is difficult to explain. The difference between the residual standard deviations is not significant. Thus it may have arisen by chance, but it is also possible that this has some connection with the greater error of method, with respect to the pressure gradient, in direct puncture than in the transseptal technique. Theoretically the difference between the residual standard deviations might be a consequence of deviations in the error of method in the determination of the variables x_1, x_3, x_5 and x_{12}, but this seems improbable.

The correlation between the observed and expected pressure gradient is shown in Figure 11. A covariation was found in par-

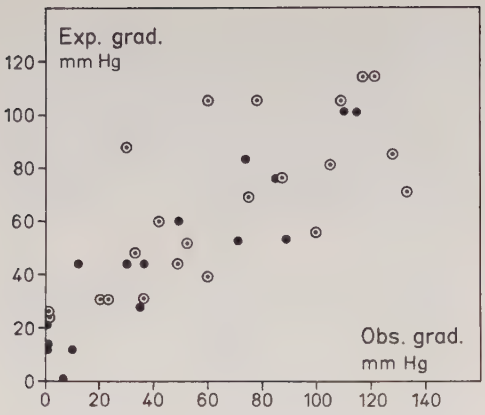

Fig. 11. The relation between the observed and the expected peak systolic gradients in cases with AS. ⊙ = puncture, ● = transseptal.

ticular for the patients investigated with the transseptal technique. The scatter was greater, on the other hand, for those in whom ventricular puncture was performed.

Discussion

In some cases a qualitatively and quantitatively correct pre-operative diagnosis can be made with the sole aid of clinical data (Ross 1959). In many cases, however, the quantitative diagnosis is erroneous, e.g. when coronary artery disease has produced pronounced symptoms in patients with slight AS (Hancock, Abelmann, Madison, Proctor & Starkey 1957, Wood 1958). The earlier discussion in this chapter showed that it is not possible to obtain sufficient information for a definite diagnosis of the degree of AS by any single method of examination. As will be shown later (cf. Fig. 16 b), signs of pronounced AS may be found angiographically in cases without a pressure gradient.

The regression analysis showed that an attempt at weighting different clinical criteria in several cases resulted in marked differences between observed and expected systolic gradient. Some difference was found in this connection, however, depending on the technique used for left ventricular catheterization. The residual standard deviation was found to be greatest for those who were investigated with ventricular puncture. This is probably connected with the effect which this method can be expected to have on the basal state. The large changes in cardiac output which may be found in connection with ventricular puncture have been shown earlier in a small number of cases (Table 8).

Conclusions

Some of the previously discussed clinical criteria of aortic stenosis were weighted by means of a multiple regression analysis. In doing this it was found preferable to take into consideration the method used for left heart catheterization. Values obtained at transseptal LHC were better correlated with the clinical findings than values from direct LV puncture. Of the variables studied it was found that clinical disability, the occurrence of dizziness on effort, the intensity of the systolic murmur and the occurrence of negative T waves in the ECG had the strongest correlation with the pressure gradient. The analysis showed some correlation between the measured and the statistically expected pressure gradient.

Chapter 5

ANGIOGRAPHIC STUDIES: METHODS

Introduction

When stenosis of the left ventricular outflow tract is suspected, measurement of the systolic pressure gradient is the most important investigation for determining whether any haemodynamically significant stenosis is present. If a pressure gradient has been demonstrated and operation has been decided upon, it is necessary in planning the operation to know not only the degree of stenosis but also its localization.

Neither supravalvular nor subvalvular aortic stenosis can be differentiated clinically from valvular stenosis with certainty (Bercu, Diettert, Danforth, Pund, Ahlvin & Belliveau 1958, Brock 1959, Kjellberg *et al.* 1959, Morrow, Waldhausen, Peters, Bloodwell & Braunwald 1959, Loogen & Vieten 1960, Braunwald *et al.* 1963). Non-valvular stenoses may be situated so near to the aortic valve that they are difficult to demonstrate solely by means of withdrawal curves (Downing 1956, Björk, Jonsson & Nordenström 1958, Brock 1959, Soulié, Joly & Carlotti 1961). Although both the altered form of the arterial pulse curve (Brachfeld & Gorlin 1959, Soulié, Degeorges, Joly, Caramanian & Carlotti 1959) and the reduced size of the arterial post-extrasystolic pulse pressure (Brockenbrough, Braunwald & Morrow 1961) may indicate subvalvular hypertrophic stenosis, the latter sign at least may also be suggested in cases of severe valvular stenosis (Beuren, Koncz & Kochsiek 1961, own observation). In hypertrophic subaortic stenosis the evaluation of the haemodynamics may be complicated by variations in the degree of the stenosis (Braunwald & Ebert 1962, Whalen, Cohen, Sumner & McIntosh 1963).

The haemodynamic investigation should therefore be complemented by a preoperative anatomical analysis. This may be done with the aid of angiocardiography or thoracic aortography, with a rapid series of exposures in two planes. With thoracic aortography an idea is also obtained of the occurrence and degree of insufficiency of the aortic valve.

My own material comprises only patients with valvular stenosis, with one possible exception (see page 111). In this condition angiographic evaluation of the valvular function is essential. Pronounced aortic insufficiency contraindicates operation in the form of commissurotomy and valvuloplasty with mobilization and decalcification of the cusps. In this type of operation, and similarly if the substitution of individual cusps by prostheses is being planned, it is of value to be able to assess the anatomy and pathophysiology pre-operatively. In congenital aortic stenosis in younger patients a perhaps ineffective commissurotomy may be avoided if thickened cusps are demonstrated beforehand. It is also of value to be able to grade any simultaneous mitral insufficiency with

the aid of angiocardiography from the left ventricle.

In the following the diagnosis of aortic valvular stenosis and of aortic insufficiency, by means of angiocardiography and thoracic aortography, will be described. Special attention will be paid both to the risk of a falsely positive diagnosis of AS and AI with the use of these methods, and to the reproducibility of the evaluations made. The results of the roentgenologic investigations on the author's own material will be given in chapter 6 in the form of some correlations with the haemodynamic and clinical findings.

Aortic stenosis

Different methods for contrast visualization of the aortic orifice and the left side of the heart

By rapid *peripheral intravenous* injection of contrast medium it is possible to visualize the left atrium, left ventricle and aorta (Robb & Steinberg 1938). With this technique secondary changes, such as those of the volumes of the left ventricle and aorta, may be seen, but as a rule no details in the aortic valve can be distinguished (Grishman *et al.* 1947).

By selective contrast injection into the *right ventricle or pulmonary artery* less dilution of the contrast medium is obtained. With this technique it is sometimes possible to distinguish details in the aortic valve (Kjellberg *et al.* 1955, Arvidsson 1958). Since as a rule the left atrium remains opaque these details can only be seen in the lateral projection. An angiocardiographic diagnosis is therefore only possible in a few cases (Kjellberg *et al.* 1955). One advantage is that the haemodynamics are affected to a lesser extent than in left ventricular angiocardiography, and volume determinations are therefore more reliable (Arvidsson 1958, 1961).

In 2 cases in this material angiocardiography was performed only in the right ventricle and pulmonary artery, respectively. Good visualization of the left ventricular outflow tract was obtained. In 4 other cases angiocardiography in the pulmonary artery had been performed some years before a left ventricular angiocardiography or thoracic aortography. In 2 of these 4 cases no details could be distinguished in the aortic valve.

Angiocardiography in the *left atrium* can be performed after transthoracic atrial puncture (Björk, Malmström & Uggla 1953, Björk & Malmström 1955) or with the transseptal technique (Brockenbrough & Braunwald 1960). With this technique, too, observations in the frontal projection will be rendered difficult by the contrast-filled left atrium.

Transthoracic atrial puncture was not used in this material but transseptal puncture with contrast injection into the left atrium was performed in 7 cases.

Angiocardiography in the *left ventricle* can be performed with different techniques: retrograde, direct puncture and transseptal.

The retrograde technique was first used in angiocardiography by Johnson *et al.* (1957) and Prioton *et al.* (1957). Some reports on cases with aortic stenosis in whom this technique was used have been published (Geissler, Porstmann & Wolt 1958, Hansson, Jönsson & Karnell 1959, Thurn, Schaede, Hilger & Düx 1960). This method was used in 7 patients in the present material.

Direct percutaneous puncture of the left ventricle with contrast injection was de-

veloped for clinical use by Ponsdomenech & Nunez (1951). This method has often been used for studies of patients with aortic stenosis (Lehman, Musser & Lykens 1957, Lehman 1959, Björk & Lodin 1959, Björk *et al.* 1961 b, Kjellberg *et al.* 1959, 1961, Grosse-Brockhoff, Löhr, Loogen & Vieten 1959, Loogen 1961, and others). It was used for the investigation of 37 patients in this material.

The transseptal technique may also be used for contrast injection into the left ventricle (Brockenbrough & Braunwald 1960, Steinhart & Endrys 1960). Apart from a few cases with aortic valvular disease (Paulin & Varnauskas 1962, MacDonald & Miller 1962, Amplatz 1962), this method appears to have been used hitherto on few series with aortic stenosis (Beuren & Apitz 1963 a, Braunwald *et al.* 1963). Left ventricular angiocardiography with a catheter introduced transseptally was performed in 9 cases in the present material.

Thoracic aortography (page 93) was the only contrast investigation performed in 6 cases in this material. These cases belonged to group ASAI.

The normal roentgenological anatomy

The aortic cusps. The mobility and thickness of normal aortic cusps have been studied in pulse duplicators (McMillan 1955), and by means of contrast injections. Detailed investigations have been made by means of thoracic aortography (Ödman 1957, Ödman & Philipsson 1958, Actis-Dato, Tarquini, Dughera, Quglia & Weisz 1959, Jefferson 1960). Similar studies have also been made with left ventricular angiocardiography (Lehman *et al.* 1957, Kjellberg *et al.* 1959, 1961, Björk & Lodin 1959). On angiocardiography or aortography normal valves are seen to open very rapidly and then to remain open, lying parallel with the aortic wall as thin, membrane-like contrast defects, often only visible as a borderline between the blood jet and the aortic contrast medium (thoracic aortography), or between the contrast jet and the blood in the aorta (left ventricular angiocardiography). The movements are so rapid that the valves are only seen during systole and diastole when they are relatively still. In diastole they form even, cranially concave arches. In cases without AI the thickness can only be assessed by left ventricular angiocardiography, and is then only $^1/_2$–1 mm, measured on the films.

Terminology. The three aortic cusps are appropriately named after their position in relation to the origin of the coronary arteries (Osler 1886), i.e. right coronary cusp (RC), left coronary cusp (LC) and non-coronary cusp (NC). The official anatomical nomenclature, i.e. right, left and posterior cusp may give rise to misunderstanding in comparisons with older studies (Davidsen, Fabricius & Husfeldt 1958).

Left ventricle. The normal thickness of the left ventricular wall, assessed by angiocardiograms, has been given as 10 mm at the most in diastole (Arvidsson 1958, Soloff & Lawrence 1962), or as 5.0–9.5 mm/m^2 body surface area (Levine, Rockoff & Braunwald 1963). The upper normal limit for the left ventricular wall thickness as seen at post-mortem has been given as 8–15 mm (Nauwerck 1912). The end-diastolic ventricular volume is said to vary normally between 50 and 150 ml, and the end-systolic volume between 20 and 40 ml (Arvidsson 1961, Dodge, Hay & Sandler 1962 a). Other authors have given the normal value for

the end-diastolic volume as 89 ± 26 ml/m^2 (Folse & Braunwald 1962) or as 100 ± 25 ml (Dodge *et al.* 1962 b).

Ascending aorta. Normally a slight systolic jet may be seen in the ascending aorta; this jet is wide and short, and directed axially. Normally the ascending part of the aorta is widest, and the whole aorta widens with increasing age, body weight or body surface area; further, other things being equal, it is larger in males (Suter 1897, Dreyer, Ray & Walker 1912, Bazett, Cotton, Laplace & Scott 1935, Dotter & Steinberg 1949, Arvidsson 1963). The diameter of the normal ascending aorta has been studied by means of angiocardiography (Dotter & Steinberg 1949). According to their figures the average cross-sectional area of the ascending aorta will be about 5 cm^2 at the age of twenty years and 7 cm^2 at the age of sixty years. These figures were obtained without regard to the heart cycle. For children normal values for the cross-sectional area in relation to the body surface area have been published (Arvidsson 1963).

Changes in aortic valvular stenosis

These appear to have been studied first by thoracic aortography (Castenfors, Hanson, Hedlund, Karnell, Lund, Philipsson, Porjé & Ödman 1956, Ödman 1957, Ödman & Philipsson 1958). A large number of studies in which left ventricular angiocardiography was used have since been made (see above).

The aortic cusps. The most important finding is reduced mobility of the cusps. All stages of transition may be found, from that in which one or more cusps become slightly dome-shaped during systole, to that in which a pronounced dome (Fig. 13) or completely immobile cusps (Fig. 14) are seen. During diastole the appearance may be normal (Fig. 15). The possibility of drawing conclusions as to a congenital or rheumatic aetiology from the angiographic findings has been discussed (Ödman 1957, Ödman & Philipsson 1958, Thurn *et al.* 1960, Jefferson 1960, Kjellberg *et al.* 1961). When thin cusps with pronounced domic formation are seen in systole, a congenital aetiology may be suspected, while rigid immobile cusps represent a final stage regardless of the aetiology.

The cusps may be of normal thickness, especially in congenital AS in younger persons (Fig. 13). Regardless of the aetiology the thickness as a rule increases with time owing to fibrosis and calcium depositions. Small calcifications may occur at an early stage (page 78). At the final stage the cusps may appear as irregular and immobile formations, several mms thick, which may even lack concavity during diastole (Fig. 14).

The annulus itself may be constricted (Ödman & Philipsson 1958), which may be of great importance with regard to the possibility of surgical therapy (Beuren & Apitz 1963 *a*). The valvular plane may also be steeply angled, so that in the frontal plane it forms a smaller angle with the longitudinal axis of the body than normally (Ödman 1957, Ödman & Philipsson 1958). In the lateral projection in these cases the left ventricle may be seen projecting over the aortic orifice, which cannot then be evaluated.

The left ventricle. The most important changes are the occurrence of hypertrophy of different degrees and dilatation of the left ventricle. Only a few angiographic studies of these changes have been published. The results will be discussed in chapter 6.

Ascending aorta. In aortic stenosis poststenotic dilatation of the ascending aorta (Fig. 13 and 16) has long been observed roentgenologically (Purks 1933–34, Grishman *et al.* 1947, Castenfors *et al.* 1956). The degree of dilatation is reported to be related to the aetiology and also to the direction of the blood jet (Ödman & Philipsson 1958, Kjellberg *et al.* 1961). In AS of long duration dilatation of the arch may also be seen. In AI more uniform dilatation of the entire aorta is observed (Ödman 1957, Ödman & Philipsson 1958). Some workers have considered that the systo-diastolic volume variations are larger than normal, especially in early cases (Ödman & Philipsson 1958, Kjellberg *et al.* 1959), while others have claimed that they lie within normal ranges (Actis-Dato *et al.* 1959). The emptying time of the ascending aorta is prolonged in AS (Ödman & Philipsson 1958, Actis-Dato *et al.* 1959).

The radiographic technique

The same *technique* was used in all examinations, and has in part been reported earlier (Björk & Lodin 1959, Björk *et al.* 1961 a). General anesthesia was not used.

The contrast medium used was 76% Urografin® in a dose of 1.0–1.2 ml/kg body weight, as a rule 60–75 ml. This was injected by means of a Gidlund automatic pressure syringe, with a pressure of 6.5 kp/cm^2. The time needed for injection varied according to the total dose and the internal diameter of the needle or catheter. The mean injection time in this material was 2.8 seconds, thus covering two to three cardiac cycles. ECG-timing was not used.

The exposures started immediately after the beginning of the contrast injection with an average delay of 0.28 seconds. The maximal exposure time was 0.03 seconds. The exposure rate was as a rule 6 frames per second for 3–4 seconds, then 1 frame per second for 10 seconds. Simultaneous exposures in the two planes were used in 1958–1959, but subsequently alternating exposures were usually used, mainly to avoid secondary radiation (Björk & Lodin 1962). One drawback with this last-mentioned technique is that comparison between the two planes becomes difficult, e.g. of the mobility of an individual cusp. Further, the calculation of the left ventricular volume will be less reliable. The maximal exposure rate, too, is rather slow in each plane, i.e. 3 frames per second. The quality of the images, however, is materially improved.

The exposures, together with an ECG lead, were marked continuously. With the alternating technique only exposures in one projection were marked. With the exception of cases investigated before 1960, the rate of the contrast injection was indicated together with the ECG and the exposures.

A two-plane automatic film changer (Elema–Schönander) was used, with a six-valve Elema Automatic 1000 CE roentgen apparatus or, for the later years, a six-valve Elema Angiomatic 1023 CE apparatus. The maximal exposure data are 300 mA at 150 KV or 1000 mA at 100 KV for the automatic 1000 CE apparatus. The corresponding values for the Angiomatic 1023 CE apparatus are 600 mA at 150 KV and 1000 mA at 100 KV.

The projections have been discussed earlier (Kjellberg *et al.* 1961, Björk *et al.* 1961 *b*). In left ventricular angiograms true frontal and lateral projections were used, with the inferior part of the thorax at a slight distance from the vertical film plane. By this adjustment the angle between the incident beam and the valvular plane in the frontal projection was lessened. In the lateral

projection no such adjustment is possible, since the valvular plane may be inclined either cranially or caudally.

Complications. These hardly include ventricular extrasystoles induced by the contrast injection. At least 1 vES was recorded in 95% of the left ventricular angiographies. A detailed account of the frequency of ventricular extrasystoles has recently been reported (Malers 1963).

Two cases with neurological symptoms after the contrast injection were noted. In one case retrograde amnesia occurred immediately after a retrograde ventricular angiography. This was transitory and had no residual effects. The other patient had general urticaria half an hour after thoracic aortography, and this was followed one hour later by signs of cerebral damage with progressively deepening unconsciousness. He died after three days. Post-mortem examination revealed an embolus in the basilar artery with malacia in the thalamus and pons. Neither of these patients had shown any reaction to the intravenous test dose of contrast medium given before the examination. A cerebral embolus was the probable cause in both cases.

In case 8 (transseptal catheterization) and case 116 (direct puncture), some contrast medium was injected into the myocardium which resulted only in a series of extrasystoles, with no clinical signs of myocardial damage.

Methods of evaluation

During the period 1958–1962 343 left ventricular angiocardiographies and 428 thoracic aortographies were performed. This material also includes 66 of the 67 cases with AS and ASAI. The results of these 771 investigations have been re-studied by the author, in collaboration with E. Malers, M.D. Special attention was paid to the above-mentioned signs of aortic stenosis and also to the occurrence of aortic insufficiency.

The evaluation comprised the mobility and thickness of the distinguishable cusps, the diameter of the orifice in systole and the occurrence of a clear jet in the ascending aorta. The maximum diameter of the ascending aorta in the lateral projection, and also the diameter of the descending aorta at the same level were measured. The measurements were made both at the systolic and end-diastolic phases. The left ventricular volume was calculated according to the formulae given by Arvidsson (1961). The diastolic wall thickness of the ventricle was measured in the frontal projection mid-way between the base and the apex.

In order to study the validity and reproducibility of the method of evaluation of the mobility of the aortic cusps, comparisons were made between the findings at angiocardiography or aortography and those at autopsy and open operations, and also between the results of repeated contrast investigations on one and the same patient. The chief aim of the comparisons with the autopsy and operation findings was to assess the risk of falsely positive diagnoses, and these comparisons were therefore made in cases with normal aortic cusps. For the comparisons between the results of repeated contrast investigations, on the other hand, all cases were included, regardless of the diagnosis.

Normal aortic cusps at autopsy. In all except one of 15 patients with mitral insufficiency who later died and at autopsy had normal aortic cusps, both left ven-

tricular angiocardiography and thoracic aortography were performed. In 11 of these 30 investigations none of the aortic cusps could be seen with certainty in systole. Out of the remaining 19 only one left ventricular angiocardiography showed suspected signs of AS, in the form of reduced mobility of two cusps. One of these two cusps appeared on aortography to have good mobility. In no fewer than 1/3 of these cases with normal aortic cusps it was not possible to evaluate the mobility of any of the cusps. While 10 out of 16 angiocardiographies gave no information in this respect, this was true for only 1 out of 14 thoracic aortographies.

Normal aortic cusps at open operation. In a group of 14 patients with pure AI information on fusion or increased thickness of the aortic cusps was not found either in the operation records or the autopsy reports. Even if there were no clinical signs of AS, it is possible that some of these patients with pronounced AI of long duration nevertheless had some increased valvular thickness which had not been noted.

On these 14 cases 13 left ventricular angiocardiographies and 15 thoracic aortographies were performed. Five of 13 angiocardiographies and five of 15 aortographies provided no information regarding the mobility of the aortic cusps. In 1 case the mobility of two cusps was observed to be slightly reduced, and in 2 cases the mobility of the LC cusp was assessed as being greatly reduced. In at least one of these 2 cases the probable reason for the impression of reduced mobility was oblique projection. Finally, in the third case misjudgement was made on a left ventricular angiocardiography in which there was no ECG recording during the contrast injection. In the remaining cases the assessable cusps exhibited normal mobility.

In summary, in spite of some uncertainty in the evaluation of individual cusps in 3 patients, there were no patients who exhibited decreased cusp mobility both on angiocardiography and aortography.

Repeated contrast investigations on the same patient. For this comparison all patients were included on whom at least two angiographies had been performed, without any intervening surgery of the aortic orifice, and with both investigations made in true frontal and lateral projections. In several patients two investigations had been performed with oblique projections (aortographies), but since the degree of obliquity may have varied, these were not included.

Altogether 208 angiocardiographies and thoracic aortographies had been performed on 95 patients. In about 50% of these patients the exposures used were simultaneous, and in the rest alternating. Otherwise the technique with regard to the number of exposures, amount of contrast medium etc. was essentially unchanged.

The results are shown in Table 28. In no fewer than 28 cases no comparison could be made because none of the three aortic cusps were visible in systole in any of the angiographies or were visible in only one. Of the remaining 67 cases, where a comparison between 3×67 individual cusps was theoretically possible, in actual fact a comparison of 149 cusps, i.e. 74%, was made. Only in 5 of these 149 compared cusp diagnoses was there any noteworthy discrepancy.

The difficulty in arriving at an evaluation of an individual cusp appeared to be greatest in the group with AI. Conflicting evaluations appeared to be more common in the group with AS. In the 3 cases where cusps

TABLE 28. *The results of comparisons between the evaluations of the mobility of aortic cusps in 95 cases, where 2–4 angiocardiograms or aortographies were performed in each case.*

Diagnosis	No. of		No. of cases where no comparison was possible	No. of cusps where a comparison was possible	No. of cusps with differing evaluation of mobility
	Investigations	Cases			
AS	29	14	3	28	3(+5)
ASAI	20	10	2	18	0
AI	29	14	7	7	0
A + M	55	25	6	39	1
M	75	32	10	57	1(+2)
Total	208	95	28	149	5(+7)

A = aortic, M = mitral valvular disease. The cusp mobility was evaluated as described on page 104.

were assessed differently, these were individual cusps in 3 different patients. In 2 of these cases, further, a long period had elapsed, i.e. 5 and 7 years respectively, between the first investigation, when the cusp was regarded as normal, and the second investigation, when it was considered to be definitely pathological. In a further 5 cases with AS there was a doubtful discrepancy between the evaluations.

In order to compare the value of different forms of investigation in the assessment of the mobility of the cusps, the material was classified according to the methods used. In 15 out of 68 angiographies performed after direct puncture, no cusp could be evaluated. The same applied to 15 out of 59 retrograde ventricular angiographies. On the other hand in 68 out of 75 thoracic aortographies at least 1 aortic cusp could be evaluated.

Of the total material of 208 angiographies the NC cusp was evaluated, with certainty or doubtfully, in 100 angiographies, the RC cusp in 166 angiographies and the LC cusp in 148 angiographies.

Discussion

Selective angiocardiography in the right side of the heart now has no place in investigations of affections in the left cardiac valves, with the possible exception of volume studies of the left atrium and ventricle. This is mainly because of the difficulties in distinguishing details, but also the fact that sufficient haemodynamic data cannot be obtained at the same time except in cases with pure mitral stenosis.

If in cases of mitral insufficiency or aortic insufficiency it is desired to compare the total with the effective stroke volume by means of volumes measured angiocardiographically, the contrast injection should preferably be given into the left atrium. Sufficient contrast density in the left atrium and ventricle is then obtained, and the volume measure is more valid than in LV angiography since arrhythmia does not usually occur in connection with the injection.

Sufficient anatomical data are also probably obtained by means of contrast injection into the left atrium to distinguish in particular between valvular and subvalvular

or supravalvular aortic stenosis. If on the other hand more detailed information is required about the thickness and mobility of the different cusps—for example if an operation with reconstruction of individual cusps is planned—the injection should be made in the ascending aorta or the left ventricle. If, further, mitral insufficiency is suspected in a case of AS, direct puncture of the left ventricle may be necessary, since it is often difficult to pass through a stenotic aortic valve with the retrograde technique (see chapter 3), and since a catheter introduced transseptally through the mitral orifice may cause false mitral insufficiency.

Urografin 76% is a contrast medium with a low incidence of side effects and low toxicity (for references see Olin 1963). The differences in viscosity and specific weight in relation to that of blood will provide no practical difficulties as regards the rate of mixing with pulsating blood, while during asystole sedimentation of contrast medium in the heart or aorta may occur (Kjellberg 1943). In order to obtain good contrast filling, it is desirable to inject as large a quantity of contrast medium as rapidly as possible. On increasing injection pressure, however, a progressively lessening increase in the contrast flow is obtained. One disadvantage with high injection pressures is stretching and recoiling of the catheter, and another is the effect which the contrast jet may have on the heart. With the percutaneous technique a catheter with an end hole is as a rule used. Even if this is furnished with three lateral holes whereby the flow rate increases and the tendency to recoiling decreases, stretching of the catheter always occurs. The recoiling may also be counteracted by using a loop-end catheter (Littman, Starobin, Hall, Matthews & Williams 1960, Paulin 1962), or by sealing the end hole (Olin 1963).

The ventricular extrasystoles which occur on left ventricular angiography appear to be unavoidable. Since they occur just as often on retrograde or transseptal angiography as on direct puncture, they are probably provoked more by the contrast jet than by the pressure of the catheter against the ventricular wall. Vain attempts have been made to reduce the frequency of extrasystoles by premedication with antiarrythmic drugs (Cullhed 1963). A more reliable way perhaps is to use catheters with less tendency to recoiling (see above), or a puncture needle without end hole (Nordenström, Figley & Sloan 1957).

The greatest disadvantage with ventricular extrasystoles occurring in close succession is that the ventricular and atrial volume determinations become uncertain (Arvidsson 1961, Sandler, Dodge, Hay & Rackley 1963). Furthermore, gradation of mitral insufficiency becomes uncertain (Malers 1963).

The severe complications which may result from left ventricular puncture with angiography have been discussed previously (Björk *et al.* 1961 a). In the two cases with cerebral emboli after retrograde catheterization this was probably due to clotting in one of the holes of the catheter, since this cannot be prevented by a continuous drip infusion during the catheterization when the tip of the catheter has several openings. Clotting such as this has also been observed after uncomplicated examinations (e.g. Adrouny, Sutherland, Griswold & Ritzmann 1963).

In the present series of cases there were no after-effects from intramyocardial contrast injections, but these do represent a

potentially hazardous complication (Smith, Wilson, Cregg & Klassen 1954, Björk *et al.* 1961 *a*). A test injection of contrast medium, controlled both fluoroscopically and by continuous ECG, should provide some protection but gives no guarantee, however, against this complication.

On evaluating the mobility and thickness of the cusps, the projection of the individual cusps must be taken into account (Ödman & Philipsson 1958, Björk *et al.* 1961 *b*, Dotter, Bristow, Menashe, Starr & Griswold 1961). Ideally the roentgen rays should be directed tangentially along the cusp so that this may be seen in profile. With the two projections used, at right angles to one another, it is usually impossible to see more than one cusp in profile. The angiocardiographic diagnosis of bicuspid aortic valves is therefore difficult (Jönsson, Brodén & Karnell 1951). Attempt should always be made to conceive the cusps "stereoscopically" so as not to obtain a falsely positive diagnosis of aortic stenosis.

Another possible reason for a falsely positive diagnosis, apart from oblique projection, is a low rate of flow, especially when ventricular extrasystoles closely succeeding one another occur with a low arterial pressure, both in normal and, in particular, in thickened aortic cusps. The risk of a falsely positive diagnosis of AS due to an exposure being made very early or late in systole is probably small, since normal aortic cusps move too rapidly to appear distinctly. Pathologically changed aortic cusps, on the other hand, may be seen to open in varying degrees (Fig. 13), especially in arrhythmias, and severe AS may then be diagnosed erroneously.

On evaluation, also, of the diameter of the orifice itself, the projection conditions must be taken into consideration. This diameter can either be measured directly between the cusps in systole, or indirectly by measuring the width of the contrast jet immediately above the aortic orifice.

The comparison between the angiographic cusp evaluation and the findings on postmortem examination or at open operation in patients with no signs of aortic stenosis showed that the risk of a falsely positive diagnosis is small. This is probably due to the rapid movements of normal aortic cusps.

The reproducibility of the evaluations is shown by the fact that the result was conflicting in only 5 of the 74 cusp diagnoses, and that in a further 7 cases the difference was doubtful. There was a relatively large number of investigations in which no definite evaluation of any of the cusps could be made, both in patients with and in those without aortic valvular disease. This also holds for 1 case with AS and for 2 cases with ASAI (see page 105).

Of the three cusps the mobility of the RC cusp could be evaluated most often and that of the NC cusp least often. This also agrees with earlier reports (Ödman & Philipsson 1958, Björk *et al.* 1961 *b*).

Of the different methods for contrast investigation, thoracic aortography seems to be the most valuable from this aspect (Prioton *et al.* 1957). In retrograde left ventricular angiography the position of the catheter in the orifice does not appear to render the evaluation more difficult to any noteworthy extent, to judge by the number of positive diagnoses made with this method, compared with direct puncture.

Conclusions

A survey is given of different methods of studying aortic stenosis with contrast in-

jection. Details in the anatomy of the aortic valve are visualized best after injection immediately proximal or distal to the aortic orifice. For studies of changes in the volume of the left ventricle the contrast injection should preferably be performed in the left atrium to avoid the arrhythmia usually seen in left ventricular angiocardiographies.

On the basis of earlier studies and the author's own findings, the appearance of the normal and the stenotic orifice, and also secondary changes in the left ventricle and ascending aorta are discussed. The technique used by the author and the principles followed in the evaluation of the angiograms are described. The evaluation of the mobility of the aortic cusps was tested in two ways. Firstly a selection was made of cases where autopsy or open operation had revealed normally mobile aortic cusps, and the angiographic and anatomical findings were compared. Secondly the reproducibility of the evaluation was examined by comparing the evaluations made on at least two different angiographies on the same patient. It was found that the risk of a falsely positive diagnosis of AS was small and that the reproducibility was good, but that a relatively large number of angiographies, especially in cases with pure AI, gave no definite information about the mobility of the cusps. From this aspect thoracic aortography appeared to be the most valuable method, and the non-coronary cusp that which most usually could not be evaluated.

Aortic stenosis with insufficiency

Methods for the evaluation of aortic insufficiency

1) *Indirect methods.* a) Dye-dilution technique after intravenous injection (Korner & Shillingford 1955). b) Plethysmography (Mackay 1960).

2) *Calculation of the regurgitant volume as the difference between the effective stroke volume and the total stroke volume,* which is determined as the difference between the end-diastolic and the end-systolic volumes. a) With radioactive roentgen contrast and praecordial scanning (Folse & Braunwald 1962). b) With angiocardiography (Dodge, Sandler & Evans 1960, Arvidsson 1961, Arvidsson & Karnell 1964), as good agreement has been shown between the stroke volume according to the Fick or the dye-dilution technique and that measured angiographically, in cases without valvular insufficiency (Gribbe 1960, Arvidsson 1961, Dodge, Hay & Sandler 1962 a).

3) *Measurement of the diastolic centripetal flow in the aorta.* a) With the dye-dilution technique (Warner & Toronto 1958, Braunwald & Morrow 1958, Rutishauser, Lüthy & Hegglin 1961, Aldridge 1962). b) With roentgen contrast (Arcilla, Agustsson, Steiger & Gasul 1961).

4) *Direct studies* of the regurgitation from the aorta to the left ventricle. a) With dye-dilution (Guidry, Wood & Burchell 1958, Armelin, Michaels, Marshall, Donald, Cheesman & Wood 1963, Malooly *et al.* 1963). b) With roentgen contrast: thoracic aortography (see below).

Although a few experiments with the methods 2 b, 3 a and 3 b have been made by the author, thoracic aortography is the routine method at this hospital.

Thoracic aortography

By using the counter-current contrast injection into a peripheral artery it is possible in small children to fill the ascending aorta with contrast medium (Castellanos & Pereiras 1939)

and also demonstrate AI (Steiner 1960), but not in older children or adults. Aortography after suprasternal puncture of the aorta has been used but is hazardous (Uricchio, Lehman, Lemmon, Titch, Boyer & Likoff 1959).

In animal experiments Rousthöi (1933) was able to demonstrate at an early date the possibility of performing both thoracic aortography and angiography from the left ventricle after retrograde catheterization of the aorta. The first thoracic aortography in man was performed by Radner (1948) after exposing the brachial artery. This method was later developed further (Brodén, Hansson & Karnell 1948, Jönsson *et al.* 1951). The introduction of the percutaneous technique (Seldinger 1953) simplified these investigations considerably (Ödman 1956, Castenfors *et al.* 1956, Johnson *et al.* 1957).

The first to have demonstrated AI in man by thoracic aortography appear to be Bustamente, Perez, Guerra & Milanes (1950). Occasional observations were reported after that date (Jönsson *et al.* 1951, Falholt, Thomsen & Davidsen 1955). Since the first reports of more systematic studies (Ödman 1957, Ödman & Philipsson 1958), a large number of investigations have been published (Porstmann & Geissler 1959, Actis-Dato *et al.* 1959, Mouquin, Brun, Chartrain, Pierron & Bacquet 1959, Dotter & Gensini 1960, Jefferson 1960, Runco, Molnar, Meckstroth & Ryan 1961, Amplatz 1962, Kjellberg *et al.* 1961, Steiner & Hollman 1962).

In principal the same *technique* has been used in this laboratory as described above for left ventricular angiography. In all adults the percutaneous technique was used, while puncture of an exposed artery was performed on the 5 cases from the Department of pediatrics. In about 50% of the material the same projections were used as in left ventricular angiography, i.e. true frontal and true lateral. In the remaining cases the patient was placed in a slightly left oblique anterior position in order to avoid projection of the aortic valve over the vertebral column (Ödman & Philipsson 1958).

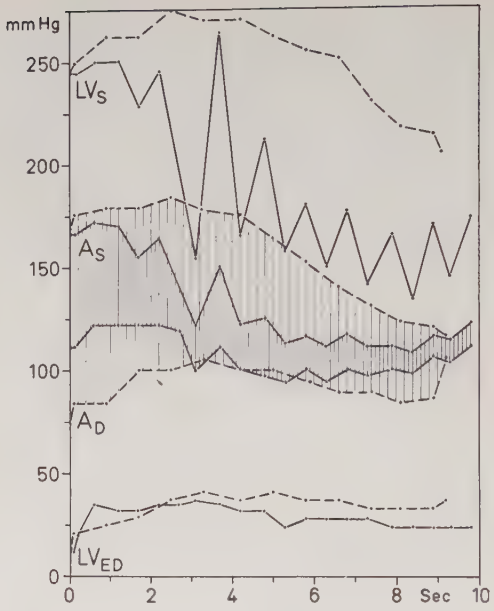

Fig. 12. The left ventricular and aortic (A) systolic (S), diastolic (D) and end-diastolic pressures during the first 10 seconds of Valsalva's manoeuvre. ——— = case A-M O (140504/63), – – – = case I J (080823/63). In case A-M O mechanical alternans was provoked, cf. Table 9.

Haemodynamic sequelae to aortography. As a rule no immediate changes in the heart rate were observed in the present series in connection with the injection, nor of the blood pressure in the few cases where this was recorded. Changes occurring before the injection due to the fact that the patient in inspiratory apnoea may have performed a Valsalva manoeuvre probably do not affect the diastolic pressure gradient, at least not during the first 10 seconds (Fig. 12). Rhythmic disturbances were also uncommon. As a rule no great changes were

TABLE 29. *The influence of asystole on the aortographic evaluation of AI in 13 cases.*

Case	Diagnosis	Asystole sec	Position of catheter tip, cm above aortic valve	Degree AI
35	AS	2.8 + 2.4 + 2.5	4	(1)
37	AS	1.9	LV	4 (false)
40	AS	2.2	RC	0
117	ASAI	7.0	NC	(4)
M-24	MI	3.5	6	0
M-125	MIMS	2.1 + 2.0	1	0–1
M-128	MSMI	4.0	2–3	0
M-218	MSMI	4.7	6	0
KN	AIMI	2.0	1	3
JA	AIMS	3.5 + 2.0	1–2	4
ME	AIMI	3.0	2	4
SL	AIMI	4.2	1	4
AE	AIMI	2.6	4	4

Symbols as in Table 28. In case 117 the contrast sedimented to the dorsal part of the ventricle. Only after the first systole was the whole ventricular cavity outlined. M- refers to a series of cases with mitral valvular disease, KN etc. to cases with combined valvular disease.

seen during the first 5 seconds of the exposure following the injection, after which moderate tachycardia and slight-moderate fall in blood pressure were observed. Out of 85 thoracic aortographies performed on patients with aortic valvular disease and in which the ECG was recorded simultaneously, one isolated vES at the most was obtained in 7 cases during the injection, and in 2 cases during the subsequent exposure.

Asystole was noted in 13 out of 428 aortographies (Table 29), including 4 cases from the author's material. Of 7 cases *without* clinical signs of AI the only one with false AI on aortography was due to the contrast being injected into the left ventricular cavity. Of 6 cases *with* a clinical diagnosis of AI the possibility of severe AI being diagnosed erroneously because of the asystole cannot be assessed with certainty. In 3 of the 4 cases from the author's material with asystole the tip of the catheter lay in a sinus in the valvular plane, and in the 4th case 4 cm above the valvular plane. Two cases were investigated in 1958–59, when it was the usual custom in this laboratory to compress the carotid arteries immediately after the commencement of the contrast injection, in order to decrease the flow of contrast medium to the brain, while 2 were investigated in 1961–62, when such compression was no longer carried out. A reflex provoked by compression of the carotid sinus is thus not probable as a common explanation.

Classification of AI

The classification that has been used in this material is based on the degree of contrast filling in the left ventricle.

Grade 1: subvalvular leakage (Fig. 17 a).

TABLE 30. *Comparisons between the aortographic and autopsy evaluations of the degree of AI in 6 cases with abnormal aortic cusps.*

Case	DM	Aortography		Autopsy	
		Position of catheter tip	Grade AI	Aortic cusps	Degree AI
M-10	+	6	(1)		—
M-309	(+)	1–2	1–2	Slightly thickened	0-mild
M-121	+	7	0		Mild
M-207	0	5	1	Thickened, slight eversion, good mobil.	—
M-216	0	2–3	(1)	Slightly thickened	Mild
BJ	+	9–10	0–1	Rigid	Pronounced

Symbols as in Table 29. DM means a basal diastolic murmur. The position of the catheter tip refers to the distance in cm above the aortic valve. In case BJ the technical quality of the angiograms was unsatisfactory.

Grade 2: the upper half of the ventricle is seen to be filled with contrast medium (Fig. 17 b).

Grade 3: the entire ventricle is seen to be contrast-filled but the contrast density is thin, considerably thinner than in the ascending aorta (Fig. 17 c).

Grade 4: as grade 3, but the contrast density is more similar to that in the aorta (Fig. 17 d).

The reliability of this classification was tested in different ways. Comparisons were made 1) between the findings at aortography and those at autopsy, 2) between the findings at aortography and those at open operation, 3) between the results of at least two aortographies on one and the same patient, 4) in order to study the degree of overlapping between groups with AI grade 3 and AI grade 4, the mean end-diastolic volume and the mean filling time of the left ventricle in these groups were compared.

Comparison between the findings at aortography and those at autopsy. The gradation of AI at autopsy is uncertain, at least that of the milder degrees. This also applies to water tests (Virchow 1893). In 14 patients, 10 of whom underwent open operation for MI, the aortic valves were evaluated both at aortography and autopsy; the water test, however, had been performed only exceptionally. In 8 cases the aortic cusps appeared normal at autopsy and competent at aortography. In 6 cases the cusps were anatomically changed, and the results of aortography are shown in Table 30.

Thus a serious underestimation of the degree of AI at aortography was made in only one case, where a poor film quality and a thin contrast density (position of the catheter tip too high) should have motivated a further aortography. In case M 207, too, the degree of AI may have been underestimated (cf. Table 31).

Comparison between the findings at aortography and those at open operation. In operations performed with the aid of extracorporeal circulation the heart is in a state of arrest, and there is a constant pressure gradient of 50–70 mm Hg from the aorta

TABLE 31. *Comparisons between the aortographic and the surgical evaluations of the degree of AI at 16 operations in 15 patients with mitral insufficiency.*

Case	DM	Aortography: Position of catheter tip	Aortography: Grade AI	Surgeon's evaluation AI	Case	DM	Aortography: Position of catheter tip	Aortography: Grade AI	Surgeon's evaluation AI
M-27	0	5	0	+	M-9	(+)	NC	1	+ + +
M-121	+	7	0	+ +	M-11	(+)	3	1	+ + +
M-216	0	2–3	(1)	+ +	M-101	0	4	1	+ + +
M-108	0	4–5	1–2	+ +	M-105	+	5–6	1	+ + +
M-111	0	3	2	+ + +	M-106	+	2	1–2	+ + +
M-116	0	5	1	+ + +			5	2	
M-205	+	6	2–3	+ + +	M-106	+	LC	2–3	+ + +
M-207	0	5	1	+ + +	BJ	+	9–10	0–1	+ + +
M-217	0	6	1–2	+ + +					
		3	2–3						

Symbols as in Table 29. + means a slight regurgitant flow, + + a moderate flow, + + + means a large flow, necessitating cross-clamping of the aorta for a total period of 19–56 minutes in these cases. The same surgeon (V. O. Björk) evaluated the degree of AI in all cases.

TABLE 32. *Repeated thoracic aortography in 19 cases, with the same degree of AI as shown by the aortograms.*

Case	Interval 1st, 2nd, 3rd aortogr.	Position of catheter tip	Degree AI	Case	Interval 1st, 2nd, 3rd aortogr.	Position of catheter tip	Degree AI	Case	Interval, 1st 2nd, 3rd aortogr.	Position of catheter tip	Degree AI
M-LV	1 w.	6–7	0	M-204	1 yr.	3–4	1	TJ	3 d.	10	3
		RC	(1)			2–3[b]	1			8	3
M-24	3 yrs.	6	0	GJ	½ yr.	4	1–2	KS	2 m.	4	3
		1[a]	(1)			5	2			2–3	3
MG	1 yr.	2–3	0	GL	1 yr.	6	2	237	10 d.	12	4
		6	0			6	2				
					2 yrs.	3	2			NC	4
GE	Succ.	5	0	ML	1 yr.	3–5	(2)	WS	4 yrs.	8	4
		2–5	0			2	(2)			6	4
GÅ	Succ.	1–2	(1)	AR	1 m.	4–5	2–3	JA	1 yr.	1–2	4
		3–4	0			7–8	2–3			NC	4
	1 w.	4	0		2 yrs.	4	2–3	IS	1 w.	Ao	4
10	7 yrs.	3	1	SR	Succ.	5	3			3–4	4
		4–5	1			7–8	3	RB	3 yrs.	4–5	4
										7	4

Symbols as in Table 29. Succ. = investigations performed in immediate succession.
[a] Slight initial injection into the left ventricle.
[b] The contrast jet was seen to reach the subvalvular region.

TABLE 33. *Repeated thoracic aortography in 14 cases, with varying degrees of AI.*

Case	Interval 1st, 2nd, 3rd aortogr.	Position of catheter tip	Degree AI	Case	Interval 1st, 2nd, 3rd aortogr.	Position of catheter tip	Degree AI	Case	Interval 1st, 2nd, 3rd aortogr.	Position of catheter tip	Degree AI
220	6 w.	3	1	106	5 m.	7	2	M-106	1 yr.	2	1–2
		1–2	0			2–3	3			5	2
M-105	2 yrs.	5–6	1	RÅ	Succ.	NC	3		1½ yrs.	LC	2–3
		5	0			6	2	303	1 yr.	6–7	3
JW	Succ.	4	1	SD	1½ yrs.	1	2			6[a]	0–3
		5	2			4–5	3		1½ yrs.	2	4
31	4 yrs.	11[a]	0	M-217	1 yr.	6	1–2	37	5 d.	Ao[b]	4
		4	2			3	2–3			7–8	2–3
TC	1 w.	4	1	IJ	1½ yrs.	3	3	M-108	1 w.	Ao[b]	4
		RC	2			5–6	1–2			4–5	1–2
	Succ.	RC	2								

Symbols as in Tables 29 and 32.
[a] Unsatisfactory film quality.
[b] Contrast injection into the left ventricle.

to the left ventricle. Even a small degree of AI may then become of great significance.

A study was made of the records of 41 operations on 40 patients with different degrees of MI. In 25 operations no AI was found. Of these the aortography showed no AI in 20 cases, while in 5 cases AI of grade (1) or 1–2 was seen. In 16 operations AI of different degrees was found (see Table 31).

Thus when AI is absent according to the aortography, no AI is usually found on open operation either, i.e. the risk of a falsely negative aortographic diagnosis of AI is small, provided that the quality of the film is satisfactory (case BJ, Table 3). AI even of grade 1 or 1–2, however, may give rise to considerable difficulties at operation in the mitral orifice. In several of these cases there was no basal diastolic murmur, but mild to moderate AI was nevertheless found.

Reproducibility of the aortographic evaluation of AI. In 27 patients two aortographies had been performed, and in 6 patients three aortographies. In 19 patients there was good agreement between the results of the investigations (see Table 32). In 14 cases there was a discrepancy between the degrees of AI found in at least two aortographies (see Table 33).

For the sake of simplicity no consideration was taken of the heart rate, the quantity of contrast medium injected or whether simultaneous or alternating exposures were used. In several cases two thoracic aortographies were performed in immediate succession. The first was then intended as a retrograde left ventricular angiography, but the catheter recoiled to the aorta. When the interval between the two investigations was long, it is obvious that changes which may have occurred in the aortic valve during this period can have caused a change in the degree of AI.

Variations of more than one grade were seen in only 4 cases, in all of which there were obvious technical reasons, e.g. injection into the left ventricle, poor film quality, or, in one case, the fact that the catheter was situated too highly (case 31). In 8 comparisons between aortographies with a maximum difference of 1 cm between the position of the catheter tip, the degree of AI was the same in 6. In 20 compared aortographies with a difference of less than 3 cm between the position of the catheter tip, the degree of AI was the same in 15. In 19 comparisons where the difference between the position of the catheter tip was at least 3 cm, the degree of AI was the same in 8. In 9 of the 16 patients with different degrees of AI, a higher degree was found with lower positions of the catheter tips. There is thus a greater risk that the gradation of AI will be affected when the difference is at least 3 cm. A relatively small number of patients in whom the evaluation varied between grade 3 and grade 4 were noted. This may be due to the fact that the differences in the degree of AI between grades 1–4 are not equal, the difference between grades 3 and 4 being larger.

The volume and filling time of the left ventricle in aortic insufficiency of grade 3 and grade 4. Such a comparison is possible when the contours of the ventricle can be distinguished. Even in cases with AI of these grades, however, the contours are sometimes blurred, which makes it difficult to determine when the ventricle is first thinly filled in diastole. Since many aortographies were exposed with the patient in the oblique position, the volumes obtained during ventricular angiography were determined. Since in the majority of these cases a series of ventricular extrasystoles were noted in association with the contrast injection, the values obtained may only be regarded as an approximate measure of the ventricular volume (Arvidsson 1961). In 2 cases where no left ventricular angiocardiography was performed, the ventricular volumes were calculated from the thoracic aortographies.

In calculating the volumes the formula for an ellipsoid was used (Arvidsson 1958, 1961). The greatest transverse diameter was used, however, and only about half of the width of the visible trabecular structure was taken into account. The filling time was estimated from the commencement of the injection to the first picture in diastole in which the left ventricle was seen to be thinly filled with contrast medium (corresponding to grade 3). The filling time was calculated as the total diastolic period. In a few cases it was possible to make this calculation from the arterial curve, but in the majority of cases only from the ECG. The time obtained was therefore only an approximate measure of the diastolic period. The total stroke volume was calculated as the difference between the end-diastolic and end-systolic ventricular volume.

The end-diastolic volume was calculated in 20 cases in the group with ASAI. It was possible to determine the diastolic filling time, as well as the total stroke volume, in 20 cases.

The results may be seen in Table 34. There is a significant difference between AI of grade 3 and grade 4 with regard to the end-diastolic volume (*), the total stroke volume (**) and the filling time (**). If a quotient is established for the rate of filling of the left ventricle, in ml/diast.sec., a probably significant difference (*) is also obtained.

TABLE 34. *The left ventricular end-diastolic volume (LV_{ED}), the filling time, the quotient between these two and the total stroke volume in grade 3 and grade 4 of AI in group ASAI.*

Degree AI	LV_{ED}, ml			LV filling time, sec			LV_{ED}/filling time, ml/sec			Total stroke volume, ml		
	M ± S.E.	S.D.	*n*	M ± S.E.	S.D.	*n*	M ± S.E.	S.D.	*n*	M ± S.E.	S.D.	*n*
3	276 ±20	60	9	1.17 ±0.12	0.35	8	264 ±41	115	8	192 ±11	35	9
4	378 ±29	98	11	0.77 ±0.07	0.23	12	561 ±112	317	8	268 ±16	53	11
Diff. 4–3	+102* ±36	—	—	−0.40** ±0.14	—	—	+297* ±119	—	—	+75** ±20	—	—

Discussion

According to the experience in this hospital, thoracic aortography has proved to be a simple and safe method in the evaluation of aortic insufficiency. The haemodynamic changes during aortography have been discussed previously (Wilder, Moscowitz & Ravitch 1956, 1957, Porstmann & Geissler 1959). These changes are probably of less significance as regards the evaluation of the degree of AI, but affect the emptying time. In experiments on dogs mild AI has been observed in connection with raised intrabronchial pressure (Nordenström 1960). In 2 cases with AS the diastolic pressure gradient over the aortic valve was shown to be essentially unchanged during a Valsalva manoeuvre.

Thus as a rule thoracic aortography does not produce any great alterations in the heart rate or rhythm. Asystole was noted, however, in a few cases. The mechanism is probably an effect of the contrast medium on the myocardium via the coronary vessels (Horger, Dotter & Steinberg 1951), since the asystole as a rule occurs too rapidly to have been provoked cerebrally, as in cerebral angiographies (Lundervold, Skraasted & Borgersen 1963). Other mechanisms have been discussed, too (cf. Malers 1963). According to the author's experience an asystole may occur without causing false AI, but may possibly cause falsely severe AI.

A number of factors may influence the aortographic grading of aortic insufficiency. *Anatomical factors* influence the contrast density, since with a wide ascending aorta there is greater dilution of the contrast medium. In the group with ASAI the diameter of the ascending aorta varied from 36 to 73 mm, corresponding to volumes of 102 and 418 ml (for an aortic length of 10 cm). The contrast density in the ascending aorta thus varies considerably, even when the quantity of contrast medium injected is relatively constant. The intermingling with contrast medium in the aorta probably takes place rapidly (Peterson, Helrich, Greene, Taylor & Choquette 1954, Swan & Beck 1960).

The contrast density in the left ventricle does not only depend on the degree of AI and the contrast density in the aorta, but

also on the volume of the left ventricle. Other factors being equal, a small ventricle fills more rapidly and has a greater contrast density than a large ventricle. The emptying capacity of the ventricle also plays a part. The greater the end-systolic volume, the greater the extent of dilution of the contrast medium and the longer the time that elapses before the ventricle is seen to be contrast-filled.

Among *haemodynamic factors* the effective flow of the heart, i.e. the flow from the left atrium in cases without mitral insufficiency, plays a certain role. The greater the stroke volume the more rapid the dilution of the contrast medium in the left ventricle and aorta. The "dilution defect" that may be seen on an angiogram in the left ventricle during diastole is situated in the central and upper posterior region of the ventricle (Kjellberg *et al.* 1961), and in pronounced AI therefore it probably does not in itself prevent also the apical regions of the left ventricle from filling with contrast medium. No investigations on the flow during aortography appear, however, to have been published.

Associated with this are the properties of the ventricle as a mixing chamber. If its properties in this respect were poor it might be expected, especially with a large residual blood volume or a large stroke volume, that the ventricle would never fill with contrast medium even in cases of severe AI. The properties of the ventricle as regards the mixing of dye solutions in experimental animals with intact aortic cusps have been questioned (Kjellberg 1943, Swan & Beck 1960, Irisawa, Wilson & Rushmer 1960), while in animals with AI it has been shown that its properties in this respect are good (Armelin *et al.* 1963). This probably also holds for the aortographic diagnosis of AI, where the regurgitating contrast medium is mixed with blood (Cliffe 1959).

In the author's material a pressure gradient was demonstrated to persist at the end of diastole (page 31). The evaluation of the degree of aortic insufficiency is usually made during the first 5–10 seconds after the beginning of the contrast injection. During this period the heart rate and rhythm are usually not materially changed (Jönsson *et al.* 1951).

Technical factors. The importance of the position of the catheter tip, in particular, has been discussed with respect to the possibilities of diagnosing false AI or falsely severe AI. No AI was shown in healthy dogs with individual film exposures (Wilder *et al.* 1956, 1957). Other authors have had the same experience (Porstmann & Geissler 1959), while the opposite result has also been reported, where with both end-hole and side-hole catheters mild AI has been observed in healthy dogs (Nelson, Molnar, Klassen & Ryan 1958). Abrams (1963), with cineangiocardiography, found a small regurgitation of contrast in protodiastole alone. This has also been confirmed with the dye-dilution technique, with which a minimal regurgitation was found in about 1/3 of the animals with healthy aortic cusps on injection immediately above the aortic orifice. This incidence increased when the injection was given just at the end of the closing stage (Armelin *et al.* 1963).

Several authors have considered that the risk of false AI in thoracic aortography performed in man is negligible (Runco *et al.* 1961, Kjellberg *et al.* 1961), while others claim that there is a risk of false mild AI (Actis-Dato *et al.* 1959, Dotter *et al.* 1961); still others have mentioned the possibility

(Ödman & Philipsson 1958, Jefferson 1960, Paulin 1962). If the tip of the catheter is situated too high in the aorta, the contrast density above the valvular plane may be too thin, especially if the aorta is wide. The same chance of a falsely negative AI is obtained by using too little contrast medium or by errors in exposure and development (see cases 31 and 303, Table 33).

Classifications according to the degree of contrast filling of the left ventricle have been made by several authors (Ödman 1957, Ödman & Philipsson 1958, Nelson *et al.* 1958, Björk & Lodin 1959, Runco *et al.* 1961, Kjellberg *et al.* 1961, Amplatz 1962, Steiner & Hollman 1962). Classification only according to the width of the regurgitating jet has also been attempted (Jefferson 1960), probably because of the small visual field in the technique used (cineangiocardiography). For those cases in whom the whole ventricle is seen to be filled with contrast medium it has been suggested that consideration should be taken of the rate at which it is filled (Ödman & Philipsson 1958, Runco *et al.* 1961). The emptying time, on the other hand (Ödman & Philipsson 1958, Björk & Lodin 1959), does not depend only on the degree of AI, but also on the cardiac output and the functional state of the left ventricle. A classification according to the rapidity with which the aorta becomes filled with contrast medium, compared with the left ventricle, has also been suggested (Steiner & Hollman 1962).

The classification used in the author's material is obviously subjective, and in some cases difficult to apply. The comparisons between the aortographic and autopsy evaluations of aortic insufficiency disclosed one case where the degree of insufficiency was seriously underestimated at aortography. This was probably due to purely technical factors, resulting in a bad image quality.

During open heart surgery, for example in operations for mitral insufficiency, it has previously been shown that even slight aortic insufficiency may become deletarious (Clauss, Buben & Altemeier 1959, Starr, Menashe & Dotter 1960, Kay, Noqueira & Zimmerman 1960). This has been corroborated in the present investigation. On the other hand, a competent aortic valve at aortography was also competent during surgery. One source of error, however, may be that pulling on the aortic orifice, either in the operation region or from cannulae, may cause deformation with false AI as a result (Virchow 1893, Kay *et al.* 1960).

In the pre-operative evaluation of mitral valvular disease a basal diastolic murmur should not be interpreted as Graham-Steell's murmur until the absence of AI has been proved (Brest, Udhoji & Likoff 1960, Runco *et al.* 1961, Runco & Booth 1963). Thoracic aortography may thus be indicated before open correction of mitral insufficiency is performed, even in cases where there is no clinical suspicion of AI.

A comparison between double investigations should show good agreement. As expected, it is found that the position of the catheter may influence the gradation, especially in AI of grades 1–3, but only to the extent, however, of one AI degree. This is in concordance with findings in animal experiments (Armelin *et al.* 1963). Falsely positive AI may perhaps be found even in investigations where there are no technical errors, but is probably always mild. In clinically certain AI its degree may vary in the same way, falsely severe or mild AI being observed, but here also probably with

only small variations. These variations need not be due, however, either to technical reasons or, where the interval between the aortographies is long, to changes in the aortic cusps. A variation in the true degree of AI may be due to fluctuations in the blood pressure and heart rate. Associated herewith are the variations in the diameter of the aortic annulus which it has been claimed may explain so-called functional aortic insufficiency (Garvin 1940, Gouley & Sickel 1943). In that case the small fenestrations in the closure lines of the aortic valve, which are found at autopsy in 63 % of all cases (Foxe 1929) may become of significance.

The comparison between AI grade 3 and grade 4 in left ventricular end-diastolic volume and filling time offered some support for the view that there is a true difference in the severity of AI between these two groups. However, it may be objected that the primary data are only approximate in several cases, and also that the material is small. The results should therefore be regarded at the moment as preliminary.

There appears to be no information regarding the size of the regurgitant flow in different degrees of AI as shown by aortography. It has been found, however, by different indirect methods, that a maximum of 60–70 % of the total stroke volume may regurgitate to the left ventricle (Braunwald & Morrow 1958, Arcilla *et al.* 1961, Sandler *et al.* 1963, Aldridge 1963).

Conclusions

The degree of severity of AI has been classified according to the degree of opacification of the left ventricle as shown by thoracic aortography. This classification, when applied on repeated aortographies on one and the same patient, has been found to have an acceptable degree of reliability, in spite of often long intervals between the two investigations, and differences in the catheter positions. Asystole does not in itself appear to constitute a source of error of any significance, and neither does any possible occurrence of the Valsalva mechanism. The position of the catheter is of influence, apart from positions in the ventricle or high above the aortic orifice, positions nearer to the orifice often, but not always, giving a somewhat higher degree of AI. The difference does not appear to be so large, however, within reasonable variations of the catheter position, that the value of the method is reduced. Falsely positive pronounced AI, of grades 3–4 as shown by aortography, can be easily discovered since as a rule this is due to the position of the catheter tip and the contrast jet. Falsely negative AI, even in cases with clinically significant AI, is due to poor film quality and/or deficient contrast filling of the ascending aorta supravalvularly.

At open operation with the aid of extracorporeal circulation, mild AI may be of great significance, while the absence of AI means competent aortic valves even during cardiac arrest.

Of the groups with pronounced AI, those with grade 4 have on an average a greater left ventricular volume with a shorter filling time than those in group 3, and similarly a greater total stroke volume, even if the measures used, for the different reasons discussed above, are only approximate.

Chapter 6

ANGIOGRAPHIC STUDIES: CORRELATIONS TO SOME CLINICAL AND HAEMODYNAMIC FACTORS

Introduction

As mentioned in the previous chapter, the angiographic picture in aortic stenosis has been described earlier. There appear, however, to have been no attempts to compare the degree of severity as evaluated by angiography, in a large series of cases, with that assessed by pressure measurements. Lehman (1959) states that the degree of stenosis cannot be predicted by the appearance of the cusps. Björk & Lodin (1959) point out that the diameter of the orifice often cannot be measured in more than one plane. Jefferson (1960) performed thoracic aortography and cineradiography in 15 cases, the majority with aortic insufficiency, and considers it probable that with the technique used aortic stenosis can be quantified in cases where the pressure gradient cannot be obtained. Steiner & Hollman (1962) claim on the basis of two cases verified at operation that the width of the jet is a good indicator of the degree of severity, which view is disputed by Amplatz (1962). We have previously reported preliminary observations on the relationship between pressure gradient and, inter alia, some angiographic findings, on a material consisting mainly of cases with combined aortic and mitral valvular disease (Björk *et al.* 1961 b).

In the following the changes in the aortic valve, ascending aorta and left ventricle, observed angiocardiographically and aortographically, are correlated with some haemodynamic and clinical data.

Aortic valve

The mobility of the cusps

As mentioned above, it is unusual to be able to form an idea of the mobility of more than one or two aortic cusps at the same contrast investigation. The certainty of this evaluation may vary from cusp to cusp in one and the same patient, even if it does not vary essentially between different investigations.

In the cases where the mobility could be evaluated, the following scale was used: unreduced, moderately reduced and greatly reduced. Since the evaluation is only quantitative with regard to the degree of stenosis, no distinction is made between cases with a thin mobile dome and those with rigid cusps, more or less immobile in systole. The following definition of the angiographic degree of stenosis has been used: *slight* stenosis: 1) where at least one cusp has good-normal mobility, 2) where 1–2 cusps have slightly-moderately reduced mobility, 3) where no cusp has greatly reduced

mobility. *Moderate* stenosis: 1) where all 3 cusps have slightly-moderately reduced mobility, or 2) where 1 cusp at the most has greatly reduced mobility. *Pronounced* stenosis: where at least 2 cusps have greatly reduced mobility and no cusp normal mobility.

In 3 cases no gradation could be made from the roentgen films, since it was not possible to evaluate the mobility of any of the cusps. Two of these 3 cases had pressure gradients of 60 and 82 mm Hg respectively; in the third case (ASAI) there was no gradient. In a further 4 cases, 3 with AS and 1 with ASAI, the evaluation of the degree of stenosis was somewhat uncertain since the mobility of only one cusp could be assessed.

The results are shown in Table 35. It is seen that of 12 cases with slight stenosis on angiography, 10 had a low and 2 a moderate pressure gradient. The cases with moderate stenosis were equally distributed among the three pressure gradient degrees. Of 35 cases with pronounced angiographic stenosis, one had a low gradient, 15 had a moderate gradient and 19 a high gradient. Of 63 cases in whom the mobility of at least 1 cusp could be evaluated, this cusp was the right coronary in 60 cases, the left coronary in 54 cases and the non-coronary in 40 cases (cf. page 92).

For the total material (AS + ASAI) the frequency of a high pressure gradient (75–152 mm Hg) was higher among cases with pronounced stenosis than among those with slight or moderate stenosis (***). The frequency of a low gradient (0–24 mm Hg) was higher among cases with slight stenosis than among those with moderate or pronounced stenosis (***).

With regard to the significance of the *aetiology* to the appearance of the aortic cusps in systole, it is difficult to compare the congenital and rheumatic aortic stenoses, since the majority of cases with rheumatic valvular disease belong to the higher age groups, where secondary changes may be found regardless of the aetiology. In one 16-year old boy (case 12) it was found, however, that the aortic stenosis was in the form of a dome with smooth mobile cusps (Fig. 15). This patient had had rheumatic fever 9 years earlier.

TABLE 35. *The angiographic degree of stenosis in relation to the pressure gradient.*

	PSG, mm Hg		
Angiography	0–24	25–74	75–152
AS			
Slight	10	2	—
Moderate	1	4	2
Pronounced	1	9	12
ASAI			
Slight	—	—	—
Moderate	6	2	1
Pronounced	—	6	7

In part of the material *anatomical analysis* was possible from autopsy or operation reports. Out of the entire material of 67 patients 8 had died, and in 7 of these autopsy had been performed. Altogether 31 patients underwent operation, 27 with the open technique. With the aid of the operation and autopsy reports it was possible in 30 cases to form an idea of the type of stenosis. On the other hand no quantitative measure of the degree of stenosis could be obtained from these data. The orifice was slit-shaped in 20 cases with 1 or 2 commissures open. Probably congenital bicuspid valves were found in 6 cases in this group. In 3 further cases, 2 of whom with pure AS, no or

TABLE 36. *The thickness of the aortic valve in relation to the pressure gradient and the presence of calcifications.*

Valvular thickness	PSG, mm Hg			Tomography	
	0–24	25–74	75–152	Calcif.	No calcif.
AS					
Normal or slightly increased	9(1)	12(1)	4(1)	5	20
Increased	—	3(3)	7(6)	10	—
ASAI					
Normal or slightly increased	1	2	2(2)	3	2
Increased	2(1)	5(2)	5(3)	11	1
AS + ASAI					
Uncertain	7(4)	3(3)	4(2)	9	5

The first figure denotes the total number of cases, the figure within brackets denotes the number of cases over 40 years of age.

negligible adhesions were found between the commissures, but the cusps were greatly calcified resulting in considerable stenosis. In one of these 3 cases, and also in one further case, the annulus was constricted (see page 86).

In 2 cases all commissures were fused to approximately the same extent, resulting in a central opening. As expected, these two cases belonged to group ASAI. In 5 cases the detailed appearance of the orifice was not stated, usually because of the large degree of calcification. In 5 cases the calcifications directly affected the myocardium, and in one case the left atrial wall and the anterior mitral cusp also.

The incidence of fusion was not the same in the three commissures. The commissure between the left coronary and the right coronary cusps was completely fused in 12 cases and partially in 4 cases, while that between the right coronary and the noncoronary cusps was completely fused in 9 cases and partially in 6 cases. The commissure between the left coronary and the noncoronary cusps was completely fused in only 4 cases, and partially in 4 cases.

The thickness of the cusps

Because of the projection conditions discussed previously, the thickness of the cusps must be evaluated with caution. When the thickness of two or three cusps, evaluated on the angiograms, was at least 2 mm, or when they were irregular, it was considered that the thickness was increased. The remaining cases were combined into one group with normal or slightly increased thickness. The results are shown in Table 36. Although a relationship was found between increased cusp thickness and high pressure gradient, the correlation between cusp thickness and age was more apparent.

In group AS the frequency of gradients exceeding 74 mm Hg was higher among

cases with increased than among those with normal or slightly increased thickness (**). In the total material (AS + ASAI) there was a higher frequency of high pressure gradients (75–152 mm Hg) among cases with increased thickness than among those with normal or slightly increased thickness (*). The frequency of increased thickness was higher among cases over than among those under 40 years of age (***).

In 14 cases no definite cusp evaluation was considered possible. This was somewhat more common in the group with a gradient of below 25 mm Hg.

Using the same gradation of the cusp thickness, comparison was made with the occurrence of calcification as observed by tomography. The younger cases where often tomography was not performed have been assigned to the groups without calcifications. As may be seen in Table 36 good agreement was found between the occurrence of thickened cusps and tomographically demonstrated calcification. The frequency of calcifications was higher among the cases with increased thickness than among those with normal or slightly increased thickness (***).

The diameter of the aortic orifice

Out of 66 cases it was possible to evaluate the diameter in both projections in 21 cases and in only one projection in 32 cases. Among these latter the measurements could be made somewhat more often in the frontal projection (20 cases) than in the lateral projection. When different measures were obtained in the two planes, the largest diameter was chosen.

A comparison between the angiographically measured diameter and the pressure gradient is shown in Table 37. It was found that of 19 patients with a gradient of at least 75 mm Hg 13 had a maximum diameter of 8 mm, and none had a greater diameter than 12 mm. Of 15 cases with a gradient below 25 mm Hg, 4 had a maximum diameter of 8 mm. Of 27 cases with a maximum diameter of 8 mm, 23 had a pressure gradient of at least 25 mm Hg, and 13 cases had a gradient of at least 75 mm Hg. In all of the 7 cases with a diameter of at least 13 mm the gradient was below 75 mm Hg.

TABLE 37. *The diameter of the aortic orifice in relation to the pressure gradient in cases with AS and ASAI.*

Diameter mm	PSG, mm Hg		
	0–24	25–74	75–152
⩽13	5	2	0
9–12	6	7	6
⩾8	4	10	13
Uncertain	4	6	3
Total	19	25	22

The figures are corrected with regard to the magnification factor. (If a circular opening is assumed a diameter of 8, 9, 12, 13 mm corresponds to a valvular area of 0.5, 0.6, 1.1 and 1.3 cm^2, respectively).

Ascending aorta

A distinct *jet* on the angiocardiograms or aortograms was found in 34 cases, and a suggestion of a jet in a further 9 cases (see Table 38). There was a higher frequency of a distinct or suggested jet in cases with a gradient of at least 75 mm Hg than among cases with a lesser gradient (*). On the other hand it was found that of 43 patients

TABLE 38. *The pressure gradient in relation to the presence of a systolic jet in 66 cases with AS and ASAI.*

Jet	PSG, mm Hg		
	0–24	25–74	75–152
Distinct	8	12	14
Suggested	3	1	5
None	8	13	2

with a distinct or suggested jet, 11 had a low gradient. In half of the cases with a gradient below 75 mm Hg, a jet was seen.

Post-stenotic dilatation

The diameter of the aorta was measured on left ventricular angiograms in the lateral projection. Measurements were made of the diameter of the middle segment of the ascending aorta and of the descending aorta at the corresponding level. In consideration of the arrhythmias that result from left ventricular angiography it would have been more suitable if the measurements could have been made at thoracic aortography. This latter investigation had not been performed, however, on all cases with AS.

The diameter was re-calculated to cm^2 aortic cross-sectional area per m^2 body surface area. The results are given in Table 39. In group AS no significant difference was found between the mean values for the aortic area in groups with different pressure gradients. Neither was any significant difference obtained when these cases were grouped according to age alone, which would have been expected in a normal material. When group AS was divided into two approximately equal groups of patients below and above the age of 30 years, respectively, no significant difference was found within these groups between those with a gradient above and those with a gradient below 50 mm Hg, as regards aortic area.

In group ASAI, on the other hand, a lower mean value for the area of the ascending aorta was found in the group with a high pressure gradient than in the group where this was low (see Table 39). The mean age in group ASAI was lower for those with a low gradient (35.2 years) than for those with a high gradient (42.4 years).

There was no significant difference between the mean value for the aortic cross-sectional area in group AS (11.8 ± 0.59 cm^2/m^2) and that in group ASAI (10.2 ± 0.72 cm^2/m^2).

In cases 24 and 113, with pressure gra-

TABLE 39. *The mean cross-sectional area (cm^2/m^2) of the ascending aorta in groups with different degrees of AS.*

	AS PSG, mm Hg			ASAI PSG, mm Hg		
	0–24	25–74	75–133	0–49	50–152	Diff.
n	12	15	13	8	15	—
M	11.5	12.1	11.8	12.7	8.9	−3.8**
S.E.	1.39	0.80	0.98	0.87	0.82	1.20
S.D.	4.81	3.08	3.55	2.46	3.18	—

dients of 109 and 152 mm Hg respectively, the aortic areas were only 6.4 and 4.8 cm^2/m^2 respectively. These two cases with no or insignificant post-stenotic dilatation, were the only ones operated on in whom the annulus was so constricted that the attempt to substitute the calcified aortic orifice with a prosthesis met with considerable technical difficulties.

To obtain some idea of whether the dilatation was confined to the ascending aorta or comprised the entire thoracic aorta, the *quotient between the diameters of the ascending and descending aorta* was calculated. Neither for group AS nor group ASAI was any correlation obtained between this quotient and the pressure gradient. In group AS, however, a lower (**) mean value was obtained for the 15 patients above 30 years of age (1.73 ± 0.07) than for the 23 cases below (2.04 ± 0.08). No such difference was observed in group ASAI. In group ASAI a lower (*) mean value was obtained for 14 cases with AI of grade 4 (1.69 ± 0.08), than for 9 cases with grade 3 AI (1.93 ± 0.06). No significant difference was obtained between the mean values for group AS (1.92 ± 0.06) and group ASAI (1.79 ± 0.06).

On *conventional cardiac roentgenography* an idea can often be obtained of the occurrence of dilatation of the ascending aorta. All of the routine cardiac roentgenograms in this material were re-studied. The occurrence of more or less pronounced bulging of the ascending aorta to the right of the mediastinal shadow was noted. The results are shown in Table 40. No attempt at quantification of the degree of dilatation was made. A significantly greater area of the ascending aorta was found in those patients where a visible aortic bulge was noted.

TABLE 40. *The mean systolic cross-sectional area (cm^2/m^2) of the ascending aorta in the groups with or without a visible aortic bulge on conventional chest radiograms (AS+ASAI).*

	Aortic bulge		
	Present	Absent	Diff.
n	30	32	—
M	12.31	9.88	−2.43**
S.E.	0.58	0.58	0.82
S.D.	3.19	3.26	—

There was some overlapping, however. In 2 out of 6 cases, for example, with an aortic area exceeding 15.0 cm^2/m^2 no post-stenotic dilatation could be shown by means of conventional cardiac roentgenograms. In 2 out of 10 cases with an aortic area of less than 9 cm^2/m^2 an aortic bulge was found.

The systolic-diastolic variations in the aortic surface area

Since one and the same difference in diameter between systole and diastole corresponds to a greater absolute increase in the cross section surface area in a wide than in a narrow aorta, this increase has been expressed as the difference between systolic and diastolic cross section surface area. In calculating the surface area, only differences in diameter exceeding 2 mm have been taken into account.

For group AS no significant difference was found between the mean values for the variations in sub-groups with different pressure gradients. On the other hand a higher (***) mean value was found for the 22 cases below the age of 30 years (3.48 ± 0.49 cm^2), compared with 18 cases above (1.18 ± 0.33 cm^2).

TABLE 41. *The mean left ventricular wall thickness (mm) in groups with different pressure gradients and left ventricular systolic pressures.*

	Pressure gradient, mm Hg								LV syst. press., mm Hg		
	AS			Diff.		ASAI			AS+ASAI		
	0–24	25–74	75–133			0–40	50–152	Diff.	100–199	200–300	Diff.
	1	2	3	2–1	3–2						
n	11	17	13	—	—	8	11	—	33	27	—
M	9.8	13.8	14.8	+4.0**	+1.0	15.1	18.8	+3.69	12.8	16.3	+3.5**
S.E.	1.04	0.89	0.95	1.37	1.31	1.70	1.04	1.99	0.79	0.72	1.07
S.D.	3.44	3.69	3.44	—	—	4.80	3.46	—	4.55	3.74	—

The figures for wall thickness are corrected for the magnification factor.

For group ASAI no corresponding correlation either to age or to the degree of AI was found. On the other hand a somewhat lower (*) mean value was obtained for the variations in the 15 patients with gradients above 50 mm Hg (2.02 ± 0.37 cm^2), compared with 8 cases with lower gradients (4.23 ± 0.85 cm^2).

There was no significant difference between the mean value for group AS (2.45 cm^2) and that for ASAI (2.77 cm^2).

Left ventricle

The left ventricular wall thickness

A comparison in 60 cases between the left ventricular lateral wall thickness measured on the angiograms and the pressure gradient is shown in Table 41. In group AS as well as in group ASAI there was a larger mean wall thickness in groups with higher pressure gradients, though the difference was not significant in group ASAI. In the total material there was a larger wall thickness in groups with a higher peak systolic left ventricular pressure.

The correlation is not improved by relating the wall thickness to the body surface area. It is probable that in healthy persons the thickness of the ventricular wall is better correlated to the total blood volume or the total haemoglobin content than to the body weight or body surface area (Sjöstrand 1957).

It would be of interest to be able to calculate the total myocardial volume of the left ventricle, since this may be considerably greater in a dilated, relatively thin-walled ventricle than in a normal-sized ventricle with thickened walls.[1] Such a calculation on the angiograms does not seem possible, however.

If the effect of any possible dilatation is disregarded, the degree of hypertrophy in patients with AS should depend not only on the degree of stenosis but also on the duration. It may therefore be of interest to compare the wall thickness with some other parameters where these two factors may conceivably be involved. The wall thickness was therefore correlated with the functional classification and the occurrence of left

[1] A sphere with an inner diameter of 5 cm and a wall thickness of 2 cm has a wall volume of 114 ml, while a sphere with an inner diameter of 10 cm and a wall thickness of 1 cm has a wall volume of 173 ml.

TABLE 42. *The functional classification and the signs of left ventricular hypertrophy in groups with different left ventricular wall thicknesses (AS + ASAI).*

LV wall mm	Total cases	Funct. classif.			No LVH			LVH				
								Only ECG				
		I	II	III + IV	ECG	Palp.	ECG + palp.	HV	VAT or T neg	Only palp.	Palp. + HV	Palp. + VAT or T neg
5–9	8	7	1	—	5	7	5	2	—	—	1	—
10–14	22	14	8	—	5	8	2	3	3	3	6	5
15–19	24	5	9	10	4	10	2	2	6	2	—	12(4)
20–28	6	1	4	1	—	1	—	—	1(1)	—	—	5(1)

Palp. = LVH at palpation. HV = High voltage, see page 72. VAT = Left ventricular activation time ≥ 0.06 sec. T neg = negative T wave in leads V_4–V_7. Figures within brackets denote cases receiving digitalis.

ventricular hypertrophy, found on palpation and by ECG (Table 42).

As a rule no functional reduction was found in those patients with a normal ventricular wall, and there was an increasing degree of functional reduction with increasing wall thickness. All patients in function class III + IV had a wall thickness of at least 15 mm. There was a higher relative frequency of function class I cases among those with a wall thickness of less than 15 mm, than among those with a thickness of at least 15 mm (***). There was, too, a higher relative frequency of function class III + IV cases among those with a wall thickness of at least 15 mm than among those with a thinner wall (***). The relative frequency of negative T waves or prolonged VAT was higher among cases with a thickness of at least 15 mm, than among those with a thinner wall (***).

The palpatory signs of hypertrophy appeared to be less sensitive but more specific than the ECG criteria used. In 9 cases no signs of hypertrophy were found, and of these, 5 had normal wall thicknesses. In those patients with signs of left ventricular hypertrophy it was found that there was good correlation between prolonged activation time or negative T waves in left precordial leads, with or without palpatory hypertrophy, and the degree of anatomical wall hypertrophy. These signs occurred in 0%, 35%, 75% and 100% of the patients in the four wall-thickness groups respectively.

Comparison with the wall thickness of the left ventricle observed at autopsy was not possible, since this was noted in only 9 of the 23 patients on whom autopsy was performed. In 4 of these 9 cases no angiographic measurement was made.

Asymmetric hypertrophy. In the case where after direct puncture of the left ventricle cardiac tamponade occurred (page 18), autopsy revealed, in addition to tight valvular aortic stenosis, that the myocardium immediately below the valvular plane was strongly developed and bulged forward somewhat into the lumen. Unfortunately the contrast injection failed in this case, and there was therefore no possibility of studying the functional anatomy of the left ventricular outflow tract. No extrasystoles were recorded in the arterial and left ventricular pressure curves. The upstroke-time of the arterial pulse curve was 0.16 sec (femoral artery).

TABLE 43. *The mean end-diastolic left ventricular volume (ml/m²) in group AS, classified according to the pressure gradient and the degree of disability.*

	PSG, mm Hg			Funct. classif.		
	0–24	25–74	75–133	I	II	III + IV
n	12	16	13	21	14	6
M	118	133	126	127	125	123
S.E.	11	12	12	8	12	27
S.D.	37	48	42	37	43	65

The differences between the means for the sub-groups within the two classification groups were not significant.

The left ventricular end-diastolic volume

The end-diastolic ventricular volume was correlated to both the systolic pressure gradient and the functional classification, for group AS (see Table 43). No significant differences between the mean values for the different groups were found.

Table 44 shows the size of the ventricular volume in group ASAI. As previously shown in the discussion of the gradation of aortic insufficiency (page 99), a significant difference was found between the mean value for the ventricular volume in those patients with grade 3 AI compared with those with grade 4. The lower figures in this Table compared with those in Table 14 are due to the fact that the volumes have been re-calculated to ml/m² body surface area. In group ASAI no significant difference was found between the mean value for ventricular volume in sub-groups with different pressure gradients or with different degrees of functional reduction.

A smaller (***) mean left ventricular end-diastolic volume was found in group AS (126 ± 7 ml/m²) than in group ASAI (185 ± 13 ml/m²).

TABLE 44. *The mean end-diastolic left ventricular volume (ml/m²) in group ASAI, classified according to degree of AI, degree of AS and degree of disability.*

	Degree AI			Degree AS PSG, mm Hg		Funct. classif.		
	AI : 3	AI : 4	Diff.	0–49	50–152	I	II	III + IV
n	9	11	—	8	12	6	8	6
M	151	214	+63**	179	190	173	171	218
S.E.	9	19	21	13	21	15	11	38
S.D.	28	65	—	37	71	37	31	93

The differences between the mean volumes in the groups with different degrees of AS or different degrees of disability were not significant.

TABLE 45. *The number of cases where aortography was performed, distributed according to the basal diastolic murmur and the relative heart volume.*

	Degree AI				
	AS			ASAI	
	0 (1)	1 1–2	2	3	4
Diast. murmur					
Not auscult.	7	2	1	1	1
Only auscult.	1	4	3	1	1
PCG	—	—	2	7	13
Heart volume ml/m²					
⩾ 500	3	2	4	6	13
< 500	5	4	2	3	2

PCG = Phonocardiogram.

Degree of aortic insufficiency

Group AS

A diastolic murmur was noted in 17 patients with AS, and in 5 of these only in the sitting position with the patient leaning forward. The murmur was recorded on phonocardiograms in 2 of these 17 cases, and also doubtfully in a further 3 cases.

In 20 cases with aortic stenosis thoracic aortography had been performed. The results of a comparison between the physical and aortographic findings, and the heart size, are shown in Table 45. In 10 of these 20 patients a murmur was heard on auscultation. It was found that of the 10 patients with diastolic murmurs all except one had mild insufficiency (grades 1–2) at aortography. The remaining patient did not show AI on aortography. Out of 10 cases without diastolic murmurs, 3 had mild aortic insufficiency.

In 23 cases of AS with auscultatory or aortographic signs of aortic insufficiency, and also in 20 cases without any of these signs, the mean indirect diastolic arterial pressure was 83 mm Hg; 10 of the 23 cases with signs of AI and 10 of the 20 cases without had a systolic pressure gradient of at least 50 mm Hg. Signs of AI were equally common in all age groups.

A tendency to increased occurrence of cardiac enlargement was found in cases with aortographic signs of AI (see Table 45). The number of observations are too small, however, to allow any detailed conclusions. No significant difference was found between the mean values for the left ventricular volume in cases with (133 ml) and without (121 ml) signs of AI. Of 3 cases with an end-diastolic LV volume of at least 200 ml/m², one case at aortography had no AI.

Group ASAI

A diastolic murmur was heard on auscultation in all except two cases. One of these (case 116) had AI of grade 4. In all cases except one the diastolic murmur was also recorded on PCG. In one further case the PCG recordings were lost.

In half of the cases with AI of grade 3, and in 13 out of 15 with AI of grade 4, the heart size exceeded 500 ml/m².

The size of the end-diastolic ventricular volume in the groups with AI of grades 3 and 4 has been given above.

Discussion

The aortic valve. An angiographic measure of the degree of severity of the stenosis may be obtained both by evaluating the mobility of the cusps and by measuring the diameter of the orifice. A comparison between the pressure gradient and the degree

of reduced mobility revealed considerable overlapping between the different groups, which may be partly explained by the fact that the angiographic evaluation was based on assessment of the mobility of all three cusps in only about two-thirds of the cases. No patient with slight stenosis at angiography, however, had a high pressure gradient, and conversely no patient with markedly reduced mobility had a low gradient. In consideration that the gradation of the mobility is subjective, the results may be said to show reasonable agreement. In a few cases, including two with a moderate to high pressure gradient, no assessment of the mobility could be made.

In consideration of the increased total systolic flow in ASAI, it might have been expected that the cases in this group with one particular angiographic degree of severity would have had higher pressure gradients than the corresponding AS group. No such tendency was observed, however.

Direct measurement of the diameter of the orifice was made in 4/5 of the cases. In about 2/5 of these the measurement could be made in two planes. Difficulty in measuring the diameter in any particular plane was more often found in the group with the highest pressure gradient. Here also some overlapping was found between the different groups; in no case with a high gradient (at least 75 mm Hg), however, did the diameter exceed 12 mm, but it was usually less than 9 mm. On the other hand some cases with a small diameter also had a low gradient.

Whether the degree of severity of the aortic stenosis was evaluated according to the mobility of the cusps or the diameter of the orifice, any patient with a high pressure gradient was assessed as having mild stenosis. In the group with a low gradient, on the other hand, a small diameter was found in a few cases, while in no case was the mobility greatly reduced.

If only the most pronounced stenoses were operated on, objective gradation with angiocardiography alone might be considered sufficient. In exceptional cases, however, this investigation yields no information on the degree of severity. Measurement of the pressure gradient is therefore essential.

It has been considered that the appearance of the stenosis can give an idea of the aetiology (Ödman & Philipsson 1958). This has been doubted by other authors (Jefferson 1960, Kjellberg *et al.* 1961). Since regardless of the aetiology secondary changes gradually occur, and since in the younger age groups those with a probably congenital aetiology naturally predominate, while definite rheumatic valvular diseases are not as a rule discovered or investigated until many years after the rheumatic fever, a direct comparison of the form of the stenosis is seldom possible. However, in one case in this material a thin dome was found in spite of a rheumatic aetiology.

The angiographic valvular thickness, as expected, depends especially on the age of the patient and not on the pressure gradient as such. With thickened or unevenly contoured valves, calcifications are also as a rule seen on tomography.

With regard to the shape of the orifice, some reports state that it is most commonly a narrow, rounded or triangular opening (Baggenstoss & Saphir 1960, Goerttler 1960). The author's own findings confirm the observations of others that these shapes are seen in particular in ASAI (McMillan 1955, McGoon, Maukin & Kirklin 1963).

In congenital AS the most common type is a slit-shaped opening (Spencer, Neill, Sank & Bahnson 1960, Ellis & Kirklin 1962, Lillehei, Levy, Varco, Wang, Adams & Anderson 1962, Gerbode, Kerth, Robinson, Ogata & Popper 1962, Morrow, Goldblatt & Braunwald 1963), as also in calcified aortic stenosis in adults (Margolies *et al.* 1931, Hall & Ichioka 1940, McMillan 1955, Bailey, Botton, Nichols, Jamison & Litwak 1956, Harken, Black, Taylor, Thrower, Soroff & Bush 1959, Gilbert, Morrow & Braunwald 1960, Edwards 1961 a). In this material a more or less slit-shaped opening was found in 77 % of the patients with AS and in 53 % of those with ASAI. It has also been confirmed in this study that fusion is most common in the commissure between the two coronary cusps, and least common between the left coronary and the non-coronary cusp (Margolies *et al.* 1931, Spencer *et al.* 1960, Edwards 1961 a, Ellis & Kirklin 1962).

Only in three patients, two of whom had pure AS, were the cusps rigid and calcified but not fused. This type should correspond to a primarily degenerative process. A few further cases of this type are possibly found in the group of five patients in whom the anatomy of the orifice could not be described in detail.

Total or partial fusion of one or more commissures is thus the general rule in AS. The aetiology may be congenital or rheumatic, since in primarily degenerative processes (Mönckeberg) only insignificant fusions are usually found ("non-bacterial thrombotic endocarditis", Wallach, Borgatta & Angrist 1962). The fact that the same commissure is most usually fused in children with congenital stenosis and in older persons with an often unknown aetiology, may be an indication that there is often a congenital aetiology even in those discovered at later ages. Other explanations are conceivable, such as congenital predisposing factors (e.g. the differences in embryology for the cusps).

The ascending aorta. Associated with the evaluation of the degree of severity is the jet sign (Castenfors *et al.* 1956), since its occurrence makes measurement of the diameter easier. In the majority of the cases with a high pressure gradient in this material a jet was seen, which, however, was also common in those with moderate and low gradients. Since a jet was equally common both in younger persons with thin cusps and in older persons with more or less pronounced calcification, it is improbable that any conclusions can be drawn from this as regards the aetiology. Opinions differ on this point, however (Ödman & Philipsson 1958, Dotter *et al.* 1961, Kjellberg *et al.* 1961). No confirmation was found in this material for the view that a jet is seen only when the stenosis takes the form of a mobile dôme (Steiner & Hollman 1962).

Localized, post-stenotic dilatation of the ascending aorta has long been observed in aortic stenosis (Kreysig 1816, Williams 1841). This was previously considered to be uncommon (Christian 1931 b, Kumpe & Bean 1948, Parkinson 1949, Mitchell *et al.* 1954, Dexter *et al.* 1958), but has been shown by other authors to be usual (Scherf & Boyd 1943, Kiloh 1950, Lewes 1951, Matthews *et al.* 1955, Tryggeseth 1958, Ödman & Philipsson 1958, Baker & Somerville 1959, Kjellberg *et al.* 1959, and others). Although Kiloh (1950) assumed that the degree of post-stenotic dilatation was proportional to the degree of severity of the stenosis, this has since been refuted (Kjell-

berg *et al.* 1959, Gillmann & Loogen 1960, Jarchow & Kincaid 1961, Loogen 1961, Amplatz 1962, Klatte 1962, Straube, McMillan, Menashe & Dotter 1963, Rockoff & Austen 1963, Lehman 1963). In cases with very pronounced dilatation cystic medial necrosis may be found (McKusick, Logue & Bahnson 1957). The different theories on the cause of post-stenotic dilatation have been discussed by several authors (Holman 1954, de Vries & van den Berg 1958, Jarchow & Kincaid 1961, Kline, Gimenez & Maloney 1962).

In the present material it is confirmed that no correlation exists between the haemodynamic degree of severity of the stenosis and the degree of post-stenotic dilatation, expressed as cm^2/m^2 BSA. In group ASAI an inverse correlation to the pressure gradient was obtained, which is difficult to explain, since the age distribution should have had an opposite effect. A possible reason may be that these cases are incompensated to a greater extent, with a lower flow velocity in systole.

The diagnosis of dilatation of the ascending aorta by means of conventional cardiac roentgenography seems to be of value, since these cases had on an average larger aortic cross-section areas than cases without this sign.

In two cases with pronounced stenosis, no or insignificant post-stenotic dilatation was found. In these cases the annulus was remarkably narrow. Similar findings have been described earlier (Bailey *et al.* 1956, Spencer *et al.* 1960, Beuren & Apitz 1963 a). The explanation for the absence of post-stenotic dilatation may be an axially directed jet (Kjellberg *et al.* 1961). The narrowing of the annulus was probably due to congenital malformation. Both because of the small dimensions and also the often pronounced calcifications with invasion of the myocardium, these cases are difficult to treat surgically.

It has been shown that in older patients with aortic stenosis, and also in cases with insufficiency, the aortic arch is also dilated (Ödman & Philipsson 1958). This was confirmed in the present material, where in group AS the quotient between the diameters of the ascending and descending aortas was lower in the older persons. In group ASAI the quotient was lower for those patients with the most pronounced insufficiency. In group AS the explanation is probably dilatation of the entire aorta due to age, and in group ASAI dilatation due to a greater total stroke volume.

In normal persons the variations in the diameter of the ascending aorta during the cardiac cycle are 1–3 mm (Gidlund & Porjé 1948, Ödman & Philipsson 1958), which corresponds to an increase in the cross section area of about 1.0–1.5 cm^2. In aortic stenosis the variations have been reported to be both increased (Ödman & Philipsson 1958) and normal (Actis-Dato *et al.* 1959). This discrepancy may be associated with the difference between different age groups. In group AS, for example, the systolic increase was considerably greater in younger than in older persons, where no certain increase was obtained. For this group, on the other hand, the size of the pressure gradient did not appear to be of importance. This was also supported by the fact that a smaller systolic increase was noted in those patients with a higher gradient in group ASAI. The number of observations is small, however.

The left ventricle. Even in the earliest descriptions of aortic stenosis, where, how-

ever, an insufficiency component may have been present, it is stated that the heart is greatly enlarged (Cowper 1705, Morgagni 1761). In aortic stenosis concentric hypertrophy of the left ventricular wall is found, and dilatation is not seen until the later stages (Baggenstoss & Saphir 1953). Cardiac enlargement is therefore commonly found in post-mortem cases (McGinn & White 1934, Kumpe & Bean 1948), but in clinical series it is especially usual in incompensated patients (Kiloh 1950, Wood 1958, Baker & Somerville 1959).

Arvidsson (1958) found a slightly increased wall thickness (9–13 mm) in cases with aortic stenosis combined with mitral valvular disease. In another study some correlation between the wall thickness and the pressure gradient was mentioned (Björk *et al.* 1961 b). The material was heterogeneous, however, and the results showed considerable overlapping. In a later study good correlation between wall thickness and peak systolic gradient was shown with wall thicknesses of up to 15 mm/m^2 BSA (Levine *et al.* 1963). It has also been found at post-mortem that the degree of wall hypertrophy is proportional to the degree of stenosis (Brown 1939, Kumpe & Bean 1948, Schiödt 1956).

In the present study significant differences were found in group AS between the mean wall thickness in those patients with a peak systolic gradient of below and above 25 mm Hg, respectively, and also in the entire material between those patients with a systolic left ventricular pressure of below and above 200 mm Hg respectively. There was a similar tendency in group ASAI, but probably because of the smallness of the material and the varying degree of dilatation the difference was not significant. The fact that there was some overlapping between the sub-groups even in group AS is to be expected, since the wall thickness is measured on left ventricular angiograms, where owing to the arrhythmia the diastolic relaxation of the myocardium may have deviated considerably from the basal level.

That an increasing wall thickness in aortic stenosis means progressive reduction in the reserve power of the myocardium is indicated by the fact that the frequency of cases with functional reduction increases in direct proportion to the wall thickness. Palpatory left ventricular hypertrophy and high voltage over the left ventricle were common in all groups with a wall thickness of at least 10 mm. The best correlation was found between wall thickness and prolonged activation time or negative T waves over the left precordium. A comparison has previously been made by several authors between increased left ventricular wall thickness as observed at autopsy, and ECG criteria of left ventricular hypertrophy (Scott, Seiwert, Simon & McGuire 1955, Allenstein & Mori 1960, Chou, Scott, Booth & McWhorter 1960, Kalliomäki *et al.* 1960, Rosenfeld *et al.* 1962). It was found as a rule that prolonged activation time was an insensitive but specific sign of LVH, that high voltage was more sensitive and somewhat less specific, and that negative T waves were the most sensitive (of the criteria used here) but the least specific. When negative T waves over the left precordium were used as a criterion, the frequency of falsely positive diagnoses was, as expected, greater in normal cases at autopsy (Allenstein & Mori 1960, Kalliomäki *et al.* 1960) than in clinically normal cases (Goulder & Kissane 1951, Scott *et al.* 1955, Chou *et al.* 1960, Rosenfeld *et al.* 1962).

Cabrera & Monroy (1952) have suggested a number of ECG criteria for the differentiation of conditions with systolic and diastolic overload. Neither they nor other authors appear to have been able to support the validity of such a classification (Cabrera & Gaxiola 1959, Sedziwy & Shillingford 1961, Selzer, Naruse, York, Kahn & Matthews 1962). Since the present material does not include cases with aortic insufficiency alone, a classification according to Cabrera's principles cannot be of any value to the discussion. It is of interest, however, that negative T waves over the left ventricle, a criterion of systolic overload, occurred 3 times as often in group ASAI as in group AS.

A study of the relationship between the angiocardiographic wall thickness and different ECG criteria of left ventricular hypertrophy has recently been published (Soloff & Lawrence 1962). Since, however, the group with a wall thickness of at least 10 mm included cases with aortic insufficiency, patent ductus and defects of the ventricular septum, and since no normal cases were investigated, it hardly seems possible to draw any definite conclusions.

In the patient in whom muscular subvalvular stenosis was also suspected, the data available were insufficient for this diagnosis to be made with certainty. Combinations of valvular and different types of subvalvular stenosis have been described (Smart 1904, Spencer *et al.* 1960, Kjellberg *et al.* 1961 and others). Brock (1957) also described a case in whom he assumed that a valvular stenosis had been complicated by secondary hypertrophic subvalvular stenosis. The same mechanism was considered to be present in a patient with discrete subvalvular stenosis, explaining the fact that in spite of an apparently radical open operation the systolic pressure gradient still remained on post-operative catheterization (Morrow & Braunwald 1959). Even if such a mechanism does occur it must, however, be rare in consideration of the large amount of data on the contraction course of the left ventricle in valvular aortic stenosis which has now been accumulated in several centres with the aid of angiocardiography.

According to post-mortem findings the size of the left ventricle in aortic stenosis has no correlation to the degree of stenosis (Kumpe & Bean 1948), and the wall hypertrophy always predominates over the dilatation in the same way as in systemic hypertension and aortic coarctation (Blondeau, Heller & Lenègre 1959). Some isolated cases with mitral and aortic stenosis showed normal ventricular volumes (Arvidsson 1961, Dodge *et al.* 1962 b), as also did cases with aortic coarctation (Arvidsson 1961, Bunnell, Ikkos, Rudhe & Swan 1961). Normal volumes are also found in cases of AS alone (Folse & Braunwald 1962, Dodge *et al.* 1962 a, Levine *et al.* 1963), although the number of observations is small. In combined ASAI, on the other hand, the ventricular volume is as a rule increased (Kjellberg *et al.* 1961, Dodge *et al.* 1962 b, Sandler 1963).

In the present material the ventricular volumes are not comparable with the normal values published, owing to arrhythmias and other factors (chapt. 5). No correlation was found between volume and degree of severity of the stenosis, and neither was there any definite correlation to the degree of functional reduction. Group AS as a whole had a lower volume than group ASAI.

The degree of aortic insufficiency. There was no difference in ventricular volume in group AS between those with and those without signs of aortic insufficiency. This, like the fact that the same mean diastolic

pressure is found, may support the justification of treating this group as homogeneous. In group ASAI a difference in ventricular volume was found in different grades of AI.

In group AS the diastolic murmur could not as a rule be recorded phonocardiographically, contrary to the case in the majority of patients with ASAI. Although there is thus some correlation between the strength of the diastolic murmur and the degree of AI, no diastolic murmur was heard in two cases with pronounced AI. Other authors have also demonstrated relatively pronounced AI in cases where this was not suspected clinically (Aldridge 1962). On the other hand, in some cases in whom a diastolic murmur was noted on auscultation, in the present study, only a minimal degree of AI was found, which has also been reported by others (Baker & Somerville 1959).

In contrast to Ödman & Philipsson (1958) it was found in this investigation that the regurgitation in ASAI is sometimes rapid and pronounced, even in cases with high systolic pressure gradients (Gorlin & Goodale 1956).

It is common in aortic stenosis to find a basal diastolic murmur without any other signs of aortic insufficiency, and this has been regarded previously as a criterion of the diagnosis of AS (page 63). In acquired stenosis the frequency is given as between 30% and 85% (McGinn & White 1934, Kumpe & Bean 1948, Leatham 1951, Aastrup & Petersen 1952, Mitchell *et al.* 1954, Wood 1958, Bouvrain & Vasselin 1958, Olesen & Warburg 1958, Baker & Somerville 1959). In congenital stenosis a lower incidence of diastolic murmur has been reported, as a rule 20%–30% (Grishman *et al.* 1947, Campbell & Kauntze 1953, Downing 1956, Nadas 1957, Keith *et al.* 1958, Wood 1958, Beuren *et al.* 1961 *b*, Braunwald *et al.* 1963). It is equally common in cases with and in those without calcifications in the aortic cusps (McGinn & White 1934, Bouvrain & Vasselin 1958). According to some authors the diastolic murmur may both appear and disappear during a long observation period (Aastrup & Petersen 1952, Campbell & Kauntze 1953, Boas 1953, Marquis & Logan 1955), but this information should be considered in the light of the fact that this murmur may be easily overlooked.

The occurrence of a basal diastolic murmur in 40% of the patients with AS in this material thus agrees with earlier findings. On the other hand no support has been found for the view that if a basal diastolic murmur is present in AS the stenosis is not mild (Kumpe & Bean 1948), or that AI is mild to moderate in cases of pronounced AS (Bergeron *et al.* 1954, Ödman 1957).

Conclusions

On a material of 42 cases with aortic stenosis without haemodynamically significant AI, and 24 cases with combined stenosis and insufficiency, angiocardiography, and in the majority thoracic aortography also, were performed. The changes observed in the aortic valve, aorta and left ventricle were recorded, and correlated with some clinical, haemodynamic and anatomical findings.

A roentgenographical evaluation of the degree of stenosis could be made more often on the basis of an assessment of the mobility of the cusps than by means of direct measurement of the diameter of the orifice in systole. The majority of the angiographically

evaluable cases with a pressure gradient of at least 75 mm Hg had signs of pronounced stenosis in the form of greatly reduced mobility of the cusps or a diameter not greater than 8 mm. In those with lower pressure gradients the angiographic evaluations showed greater variations.

A jet was seen in most cases, but this in itself yielded no information as to the degree or form of the stenosis, or probably of the aetiology. Thickened cusps were seen in patients of higher ages, and tomography in these cases showed as a rule calcified cusps. In those patients in whom anatomical analysis was made (at open operation or autopsy), it was verified that a slit-shaped opening is usually seen in aortic stenosis, due to either congenital or acquired fusion between 1–2 cusps. This supports the view that "acquired" stenosis is more likely to have a congenital or rheumatic aetiology than to be due to primary atheroma. Since it is the same commissure, between the coronary cusps, that is most usually fused, a congenital aetiology can be suspected in several of the cases discovered at adult ages.

The degree of post-stenotic dilatation of the ascending aorta is not correlated to the degree of stenosis. The difference between the diameters of the ascending and descending thoracic aorta is greatest in younger patients. The systo-diastolic variations in the calibre of the ascending aorta are independent of the pressure gradient but are greatest in the younger persons, probably due to the greater elasticity of the aortic wall.

In two cases a hypoplastic, greatly calcified annulus was seen in combination with the absence of or insignificant post-stenotic dilatation. It is important to observe such cases, since these conditions may mean technical difficulties at operation.

The wall thickness of the left ventricle is correlated both to the pressure gradient and to signs of hypertrophy according to palpation and ECG. The strongest relationship was found between increased wall thickness and the occurrence of prolonged activation time or negative T waves over the left ventricle.

The end-diastolic volume of the left ventricle, measured approximately on the angiocardiograms, was not correlated either to the pressure gradient or the degree of subjective functional reduction. In group AS this volume was not greater in those patients in whom auscultation or aortography revealed signs of mild AI. It was, on the other hand, greater in those with ASAI, and within this group it was greatest in pronounced AI (grade 4). In cases with AS the diastolic murmur as a sign of aortic insufficiency was as a rule only detected on auscultation, but in those with ASAI it could also be recorded on PCG. In exceptional cases this sign was absent in spite of pronounced aortic insufficiency.

Chapter 7

GENERAL SUMMARY

The aim of this work was to study the haemodynamic, clinical and angiographic changes in a series of cases with aortic valvular stenosis. The patients were referred to this hospital for pre-operative evaluation during a five-year period. The material was divided into two diagnostic groups, patients with pure stenosis or stenosis with slight insufficiency (AS) and patients with stenosis and pronounced insufficiency (ASAI). The degree of stenosis was classified according to the pressure gradient (peak systolic gradient at rest), and the degree of insufficiency according to the findings at thoracic aortography in the majority of the cases. The material was also classified according to the degree of clinical disability.

Cases without clinical disability and cases without symptoms had as a rule a low or moderate pressure gradient, but a high gradient was found in a few cases. All cases with pronounced disability had a moderate or high gradient. Cases with AS were most frequent in the age groups 7–24 years and 45–66 years while cases with ASAI occurred in the age group 35–54 years. This difference in age distribution may be connected with the principles of selection, but also with differences in aetiology and prognosis in AS and ASAI. A congenital aetiology was more frequent in AS, while a history of rheumatic fever was more usual in ASAI. In those cases where the anatomy could be studied at open operation or autopsy, it was confirmed that in aortic stenosis the orifice is as a rule slit-shaped, with fusion of one or two commissures. A purely degenerative aetiology, as described by Mönckeberg, thus seems to be rare. Hypercholesterolaemia was found in two cases, probably without causal relationship to the valvular disease.

The degree of stenosis is commonly expressed as the peak systolic gradient, though the calculation of the aortic valve area is also used in cases without valvular insufficiency, with simultaneous determination of the cardiac output and pressure gradient. In the present material the peak systolic gradient has generally been used. This is because of the fact that the cardiac output was not measured in all cases, and that in cases with ASAI the total output cannot as yet be accurately determined. However, in published series of cases with aortic stenosis a fair agreement was found between these two measures of the severity of stenosis. In principle the cardiac output and pressure gradient should be measured simultaneously. In cases with gross abnormalities of cardiac output or heart rate the valve area can then be calculated according to the formula described by Gorlin & Gorlin (1951), or a somewhat simplified version described here. In determining the pressure gradient the choice of systemic artery does not seem to be of great importance, though the central aortic pressure is to be preferred.

On the other hand determination of the pressure gradient at operation, after thoracotomy, seems to be of limited value as a measure of valvular resistance, since the flow factor may vary considerably from case to case.

In the evaluation of the haemodynamics at rest it was found that the end-diastolic left ventricular pressure, the pulmonary artery and pulmonary artery wedge pressures, and the cardiac output and stroke volume, showed correlation with the degree of clinical disability but usually not with the degree of objective severity. Thus the circulatory adaptation was not dependent only on the degree of stenosis *per se*, but also on the functional state of the left ventricular myocardium, a factor which depends on both the degree and the duration of the stenosis, and on complicating diseases such as myocarditis or coronary sclerosis. Consequently, a normal cardiac output and stroke volume, as well as normal pulmonary artery pressures, may be found even in cases with a high pressure gradient, until symptoms with functional reduction appear. This will usually not happen until middle age or later. Here the normal variations with age should be kept in mind. For several reasons the end-diastolic left ventricular pressure could not be proven to be a valid index of the degree of compensation of the left ventricle in this material. Pulsus alternans was found in 10% of the cases and it was confirmed that this is a sign of severe stenosis.

In a limited part of this material the alterations at exercise could be studied during both right and left heart catheterization. As could be expected from the pressure-flow relationship the pressure gradient remained low in all cases with a low gradient at rest, except one patient with ASAI where a very marked rise in the effective cardiac output occurred. In cases with a moderate or high gradient at rest, the gradient rose markedly in all cases where the cardiac output increased. In the larger part of the material, however, the effect of exercise was only studied during right heart catheterization. As a rule the cardiac output increased normally in relation to the increase in oxygen uptake. In many cases, all with a high or moderate pressure gradient at rest, and the majority above 40 years of age, the cardiac output increased within the lower range for normal persons. During the muscular work performed, which resulted in highest attained heart rates of only about 130 beats/min, there were no consistent changes in the stroke volume and therefore an increase in cardiac output resulted. This increase was present even in the third of the cases where pulmonary hypertension was noted during exercise and, in most of these cases, also at rest.

All symptoms were more frequent in group ASAI than in group AS, with the exception of dizziness and syncope on effort, which were rare in group ASAI. Effort dyspnoea was found to be a sensitive but unspecific sign of the degree of severity of stenosis, while chest pain on effort and dizziness on effort were less sensitive but more specific in this respect. There is a large variation in survival time after the onset of dyspnoea and chest pain. The prognosis after the onset of dizziness on effort and signs of left ventricular failure is more grave. The patho-physiology of the symptoms is discussed. Autopsy findings in a series of cases from this material confirm that chest pain in aortic stenosis is as a rule not caused by coronary artery disease.

Among the findings in group AS at physical examination palpatory left ventricular hypertrophy, an absent or diminished second heart sound, and a grade 4–6 basal systolic murmur with long duration and its maximum in the second half of systole were more frequent in groups with higher pressure gradients. In group ASAI a similar correlation was found only for the quality of the second heart sound. Within group AS the difference in the occurrence of the typical physical signs was more distinct between the groups with low and moderate gradients than between those with moderate and high gradients. The mean indirect brachial artery pressures showed no significant differences between AS groups with different gradients. Within group ASAI there was a lower mean diastolic pressure in the group with the most pronounced AI. The mean pulse pressure was lower in group AS than in group ASAI.

High voltage as the only electrocardiographic sign of left ventricular hypertrophy occurred in a third of the AS cases with a low pressure gradient. In group ASAI prolonged left ventricular activation time and negative T waves over the left precordium occurred in a high frequency in groups with different degrees of severity. Although ECG signs of left ventricular hypertrophy occurred in increasing frequency with increasing pressure gradients in group AS, a normal ECG or an ECG with normal T waves over the left precordium could be found even in cases with a high gradient.

Signs of pulmonary congestion on chest radiograms were not observed in this material. In some cases the right ventricle or left atrium was enlarged; in all these cases pulmonary hypertension was observed but this was also present in some cases without enlargement of these chambers. Signs of enlargement of the left ventricle occurred equally often in AS and ASAI, and showed stronger correlation to the occurrence of general heart enlargement than to the degree of stenosis. An increased relative heart volume was found more often in ASAI than in AS, and more often in patients over 40 years old, but the heart volume was not correlated to the degree of stenosis. Calcifications were shown by means of tomography in 37 cases. Among the patients below 40 years of age calcifications occurred especially in those with a moderate-high pressure gradient, while they were common in patients above this age regardless of the size of the gradient.

The correlation between the pressure gradient and some clinical symptoms and signs was studied by means of multiple regression analysis. A co-variation for the statistically expected and the actually measured pressure gradient was demonstrated. A difference in this respect was found between those cases where the gradient was determined with the transseptal technique and those where direct puncture was used. This probably reflects the difference in influence on the basal state of these two methods.

The essential angiographic finding in aortic stenosis is decreased mobility of the aortic cusps. In cases with normal aortic cusps observed at autopsy (mitral valvular disease) or open heart surgery (aortic insufficiency) the risk of a false diagnosis of aortic stenosis was found to be small. In all but a few cases on whom at least two angiographic examinations had been performed the reproducibility of the evaluation of the degree of mobility was good. As a rule more information regarding the mobility of the cusps was obtained by thoracic

aortography than by left atrial or left ventricular angiocardiography. Of the three aortic cusps the non-coronary was the one most difficult to evaluate.

The degree of severity of aortic insufficiency has been classified into four grades according to the degree to which the left ventricle was contrast-filled at thoracic aortography. Among factors influencing this evaluation the position of the catheter tip is the one most discussed. A falsely positive diagnosis of aortic insufficiency seems rare and as a rule easily disclosed as due to direct injection into the left ventricle. A falsely negative diagnosis may be found in cases where the position of the catheter tip is too high, or due to other technical errors, resulting in a low contrast density above the aortic valve. In a series of cases where at least two aortographies were performed on the same patient variations in the position of the catheter tip resulted only in slight differences in the aortographic degree of aortic insufficiency. Even a slight degree of aortic insufficiency at aortography is of clinical importance as it may mean a significant problem at open heart surgery for mitral insufficiency. Preliminary observations suggest a correlation between the degree of insufficiency and the end-diastolic volume and the filling-time of the left ventricle.

The different angiographic findings in the author's material have been correlated to the peak systolic gradient. The mobility of the cusps could be assessed in most cases, and was found to be correlated to the pressure gradient. In a few cases the mobility could not be evaluated. This difficulty in evaluation, due to oblique projections, was more common in the assessment of the cusp thickness and the diameter of the orifice. The cusp thickness was better correlated to the age of the patient than to the pressure gradient. In cases with thickened cusps calcifications were as a rule found at tomography. In the majority the diameter could be measured only in one plane. A small diameter was found in all cases with a high gradient, but also in cases with a low gradient.

A jet was seen slightly more commonly in cases with a high gradient. There was no significant difference between the mean cross-sectional area of the ascending aorta in groups with different pressure gradients. Nor was there any significant difference in this respect between groups AS and ASAI. The mean quotient between the diameters of the ascending and descending thoracic aorta was lower among older cases but was not correlated to the pressure gradient. The same applied to the systolic-diastolic variations in cross-sectional area, which were larger among younger cases with a more distensible aortic wall. An aortic bulge on the frontal chest radiogram means as a rule a dilated ascending aorta, though there are falsely positive as well as falsely negative cases.

The mean left ventricular wall thickness increased with increasing pressure gradients and systolic left ventricular pressure. All cases with pronounced functional reduction had increased wall thickness, while this was uncommon in cases without functional reduction. With a few exceptions palpatory and electrocardiographic signs of left ventricular hypertrophy were absent only in cases with a normal wall thickness. Prolonged activation time or negative T waves over the left precordium increased in frequency with increasing wall thickness. The wall thickness should thus be regarded as

an expression of degree as well as duration of stenosis. The mean end-diastolic left ventricular volume was not significantly different in groups with different degrees of stenosis, nor in groups with different degrees of disability. The volumes in the groups with the most pronounced disability varied greatly, however. The end-diastolic volume was larger in ASAI than in AS, as could be expected with regard to the larger total stroke volume.

In a few cases no diastolic murmur was heard on auscultation in spite of the presence of aortic insufficiency. The murmur as a rule increased in intensity with increasing degrees of regurgitation. When a diastolic murmur was recorded on the phonocardiogram, the insufficiency was as a rule pronounced. In group AS an increased relative heart volume was found in a few cases without aortic insufficiency or with slight insufficiency. On the other hand, pronounced insufficiency was present in some cases with a normal heart volume.

APPENDIX 1

Statistical Methods

Notation

Number of patients (cases) $= n$.

$$\text{Mean: } M = \frac{\sum x_i}{n},$$

where x_i denotes the ith recorded value in a series of n values.

Standard deviation

$$\text{S.D.} = \sqrt{\frac{\sum (x_i - M)^2}{n}}.$$

Standard error of the mean

$$\text{S.E.} = \frac{\text{S.D.}}{\sqrt{n-1}}.$$

Standard error of a difference between two means

$$\text{S.E.} = \sqrt{\text{S.E.}_1^2 + \text{S.E.}_2^2}.$$

Multiple regression analysis

Linear regression analysis was performed. A variate, y, is considered as a linear function of a number of variables: i.e. $y = a + bx + cz + du + ev$, etc.

The coefficients a,b,c etc. were calculated according to the least square principle (cf. Snedecor 1956).

Significance tests

The following significance tests were used:

1. In percentage differences: x^2-test with one degree of freedom. Yates' correction was used.

2. In mean differences between groups: Student's t-test

$$t = \frac{M_1 - M_2}{\sqrt{\text{S.E.}_1^2 + \text{S.E.}_2^2}}.$$

3. In comparisons, expressed by intra-individual differences (d_i)

$$t = \frac{\frac{\sum d_i}{n}}{\sqrt{\frac{\sum d_i^2 - \frac{(\sum d_i)^2}{n}}{n(n-1)}}}.$$

4. Correlation and regression coefficients were tested according to Hald (1948).

Significance levels

Analyses of significance have been made chiefly in conjunction with the tables. The term "significant" is used in accordance with the following convention. If an observed difference between two means is of such magnitude that the probability P of obtaining a difference at least equal to the observed value is greater than 0.05 (where the null hypothesis is assumed to hold), the observed difference is said to be *non-significant*.

If $0.01 < P \leqslant 0.05$ the difference is said to be (*almost*) *significant* and is denoted by *.

If $0.001 < P \leqslant 0.01$ the difference is said to be *significant* and is denoted **.

If $0.001 \geqslant P$ the difference is said to be (*highly*) *significant* and is denoted ***.

Statistician: Gunnar Eklund, Ph.D.

APPENDIX 2

For reasons discussed in the text case histories are given for seven cases.

Case 6. 13-year old girl who had never managed to do as much as other children of her age. Valvular heart disease discovered when she was 7 years old, and since that time she had also had chest pain on effort. Status: not incompensated. Basal systolic murmur of grade 5. ECG: negative T waves in AVF, V5 and V6. Chest radiogram: heart volume 410 ml (320 ml/m^2). RHC: normal pressures, CI 3.1 l/min·m^2. The transseptal technique had not then been started at this hospital. Since the clinical picture was clear and the anatomy had been studied by angiocardiography from the pulmonary artery, operation was decided upon. At operation a systolic pressure gradient of 42 mm Hg was found. Only one commissure was open and the cusps were thickened. One year post-operatively: no subjective symptoms and the patient had increased 10 kg in weight. Basal systolic murmur of grade III–IV. ECG: low and biphasic T waves in V6 and V7. Heart volume 460 ml (330 ml/m^2). On catheterization a systolic pressure gradient of 49 mm Hg at rest, increasing to 120 mm Hg during exercise was found. At the same time the flow increased from 3.1 to 5.6 l/min·m^2. Aortography: no AI.

Case 17. 18-year old schoolgirl with no history of rheumatic disease. Murmur discovered at the age of 8 years. Breathless on exertion for the last 4 years. For 6 months she had been disabled by dyspnoea, dizziness, palpitations and chest pain on slight exertion. She was referred to this hospital as a case of aortic valvular disease with impending left ventricular failure. Physical signs of ASAI. ECG normal. Chest radiogram: heart volume 520 ml (330 ml/m^2). RHC: normal pressure at rest and during exercise, CI 4.4 l/min·m^2, SV 50 ml, AVD 32.8 m/l. LHC: systolic pressure gradient of 14 mm Hg. Angiocardiography and aortography: AS + mild AI (grade 1, Fig. 17). At follow-up examination 2 $^1/_2$ years later there were no subjective symptoms but the objective findings were unchanged.

Case 25. 38-year old, unmarried machinist with no history of rheumatic disease. For the last 18 years he had had tiredness and shortness of breath, and for a similar length of time had been known to have a heart disorder. Chest pains at rest for the last 3 years. Physical signs of AS. Chest radiogram: heart volume 650 ml (340 ml/m^2). ECG first showed sinus tachycardia and negative T waves over the left precordium, but was normal 2 months later. RHC and LHC: no systolic pressure gradient (see Table 12). Angiocardiography and aortography: AS without AI (Fig. 16). Two years later subjectively unchanged. Had continued work as usual the whole time.

Case 33. 53-year old caretaker with no history of rheumatic fever. Heart enlargement and systolic murmur discovered 1955. No heart symptoms at that time, and rhythm regular. In 1957 he had an attack of influenza, during which he began to have palpitations and moderate dyspnoea on effort. On admission (1958), no signs of incompensation. Basal grade 3 systolic murmur, no diastolic murmur. Chest radiogram: heart volume 1290 ml (660 ml/m^2). Tomography showed pronounced calcifications at the position of the aortic valve. ECG: atrial fibrillation. RHC: normal pressures at rest. LHC: no pressure gradient. Angiocardiography showed signs of AS and pronounced dilatation of the whole thoracic aorta. 5 years later almost completely free from symptoms. The systolic murmur was unchanged, and a faint basal diastolic murmur could be heard in the sitting position. Heart

volume: 1450 ml (730 ml/m²). RHC and LHC, see Table 12. Angiocardiography and thoracic aortography showed slight AS and grade 2 AI.

Case 109. 37-year old unmarried machinist with relatively heavy work. Rheumatic fever 1928 and 1942. Valvular disorder discovered in 1958 in connection with burn injuries. Stated then that he had no heart symptoms. Physical signs of AS and AI. ECG: prolonged VAT and negative T waves over the left precordium. Chest radiogram: heart volume 1250 ml (720 ml/m²). RHC: pulmonary artery mean pressure 25 mm Hg, which during slight exercise (200 kpm/min) rose to 42 mm Hg. CI not determined. LHC: systolic pressure gradient 49 mm Hg. Angiocardiography and aortography: AS+ grade 3 AI. 4 years later he still said that he was free from symptoms and refused follow-up examination. After a further 6 months he had a "chill" with shortness of breath and orthopnoea. On re-admission he had congestive heart failure and died after one month. Autopsy revealed a rigid calcified aortic valve with tight stenosis. Heart weight 875 g. with considerable hypertrophy of both ventricles.

Case 118. 49-year old man in whom heart disorder was discovered at the age of 16 years. Rheumatic fever at 32 years. For the last 5 years he had had shortness of breath, palpitations and chest pain. Status: not incompensated. Basal systolic murmur of grade 4–5, diastolic murmur at the left sternal border. ECG: negative T waves in V4, V5 and AVL. Chest radiogram: heart volume 1390 ml (760 ml/m²). Tomography: large calcium deposits in the aortic cusps. RHC: PAW pressure 27 mm Hg, CI 3.9 l/min·m². Catheterization of the left ventricle was unsuccessful, both by the retrograde and the transseptal techniques. Aortography showed pronounced aortic insufficiency and aortic stenosis. At operation the aortic valve was found to be transformed to a calcified block which continued to the anterior mitral valve. Before aortotomy the mean pressure in the left atrium was 39 mm Hg, and the LV end-diastolic pressure 33 mm Hg. The systolic pressure gradient was only 26 mm Hg. The patient died.

Case 120. 46-year old man with nocturnal orthopnoea for the last 3 years. Physical signs of AS, AI, MS. Chest radiogram: heart volume 1250 ml (730 ml/m²). ECG: atrial fibrillation. RHC: normal resting pressures. CI not determined. LHC: systolic pressure gradient 16 mm Hg. Angiocardiography: AS+grade 3 AI. At transventricular operation mild MS and AS were found, and the latter was dilated. The patient did not improve and died one year later. Autopsy was not performed.

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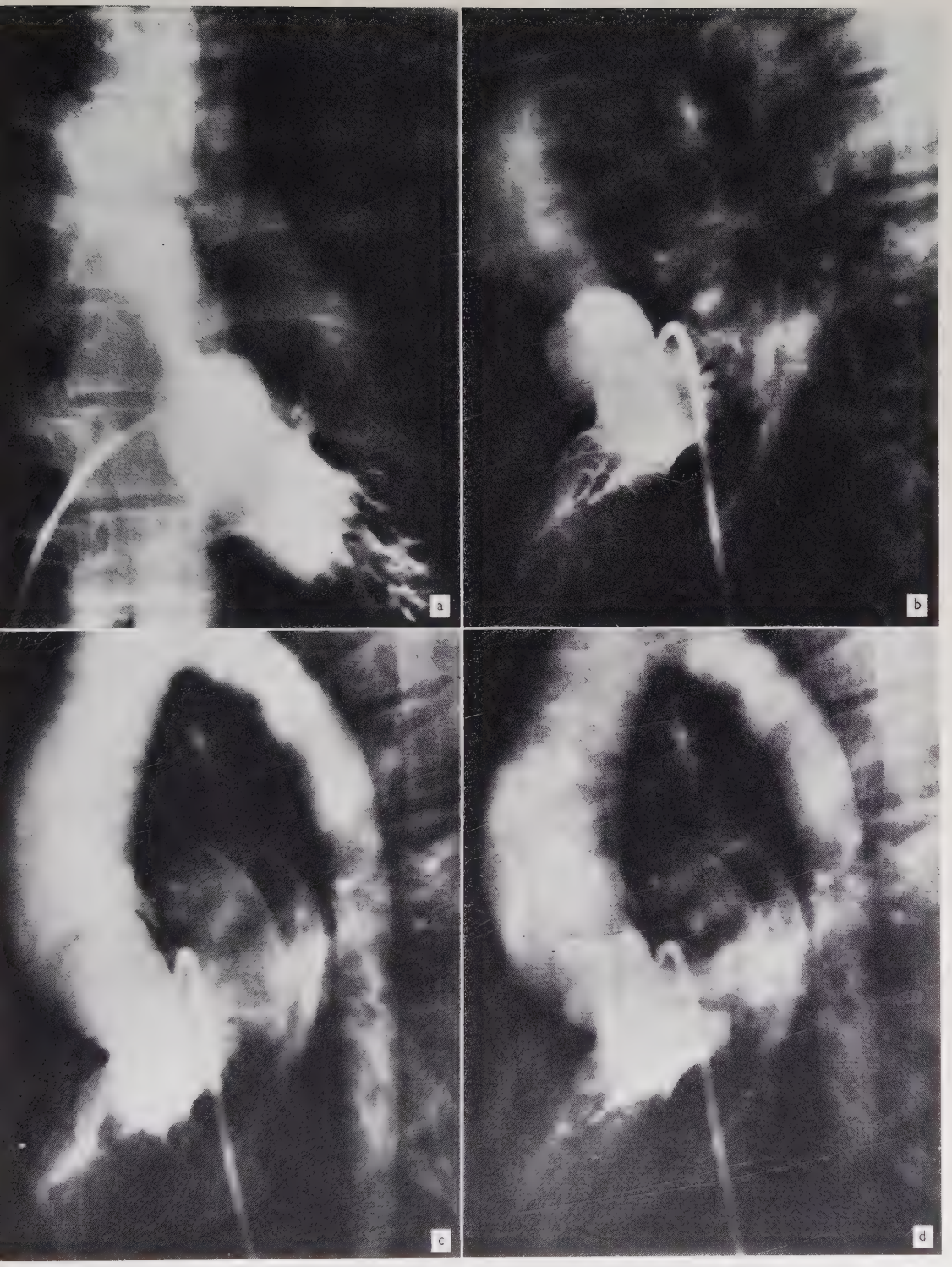

Fig. 13. Case 11, PSG 85 mm Hg. Left ventricular angiocardiography. *a*, Systole, frontal projection. A distinct jet is seen. *b*, Systole, lateral projection, exposed simultaneously with *a*. The jet is broad and not distinct. *c*, Systole, lateral projection. Thin cusps with pronounced dome. Post-stenotic dilatation of the ascending aorta. *d*, Late systole, lateral projection. The cusps are half open.

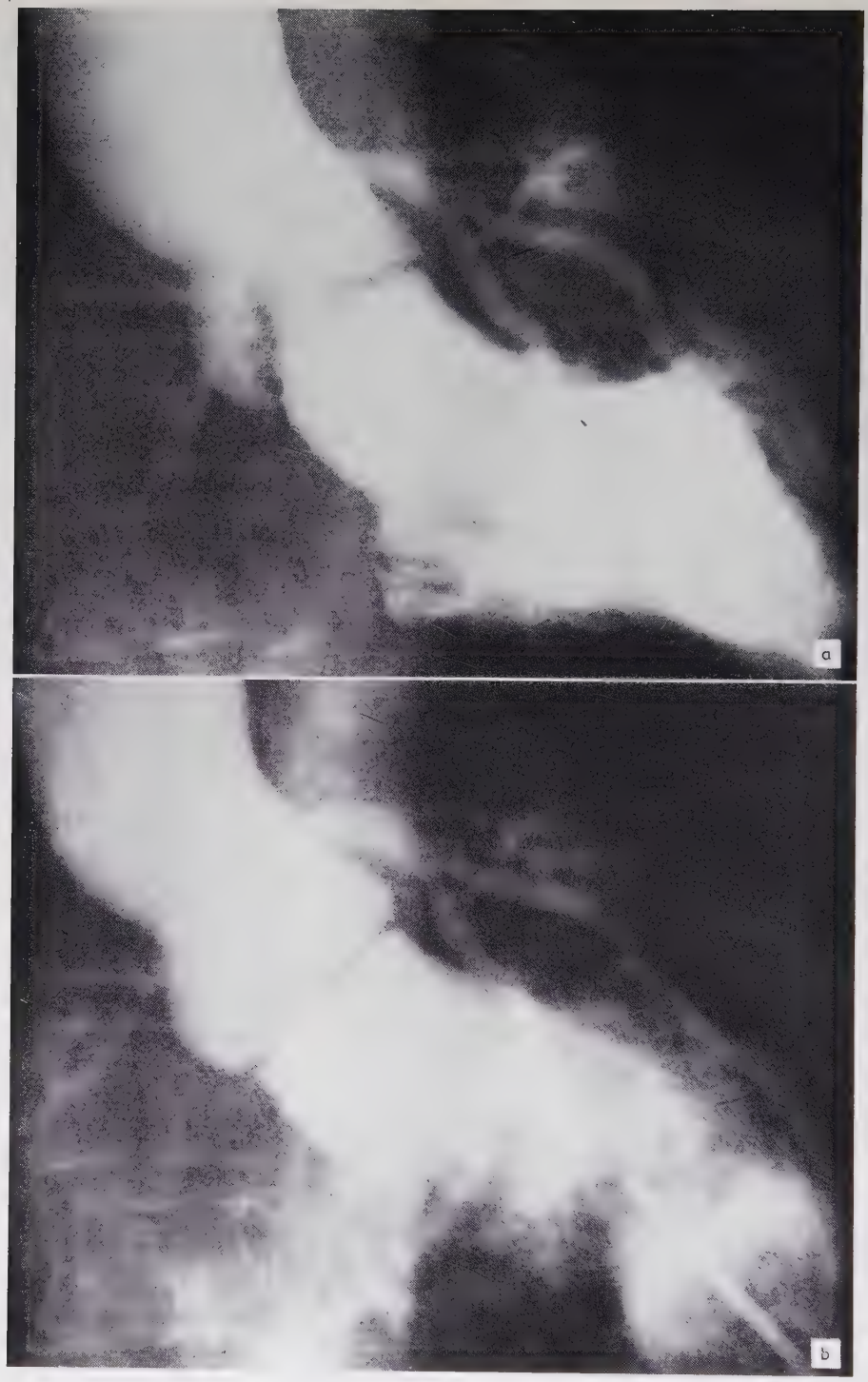

Fig. 14. Case 34, PSG 78 mm Hg. Left ventricular angiocardiography. *a*, Systole. The RC cusp is partly open, the LC cusp is immobile. Both cusps are thickened and irregular. *b*, Diastole. Absence of normal concave form.

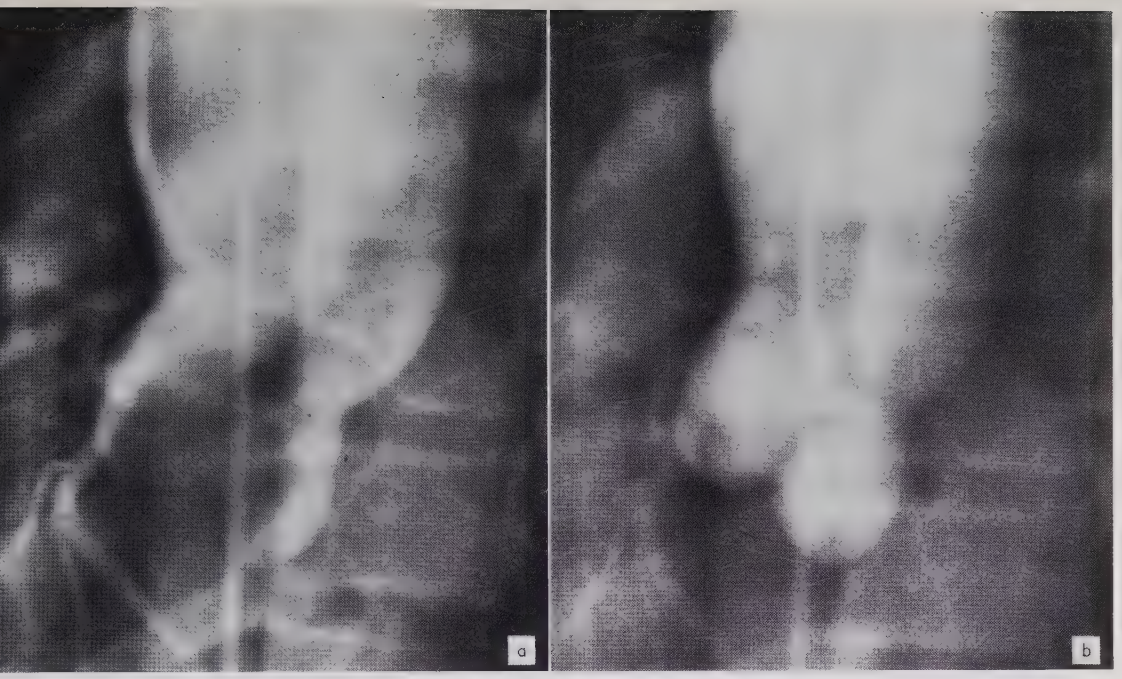

Fig. 15. Case 12, PSG 62 mm Hg. Thoracic aortography. *a*, Systole. Smooth mobile cusps with dome. Dilated ascending aorta with a jet on the right of the picture. *b*, Diastole. The cusps appear normal.

Fig. 16. *a*, Case 19, PSG 33 mm Hg. Left ventricular angiocardiography, systole. Eccentric jet. Pronounced post-stenotic dilatation.

Fig. 16. *b*, Case 25, PSG 0 mm Hg. Thoracic aortography, systole. Narrow eccentric jet, suggested whirls in the dilated ascending aorta.

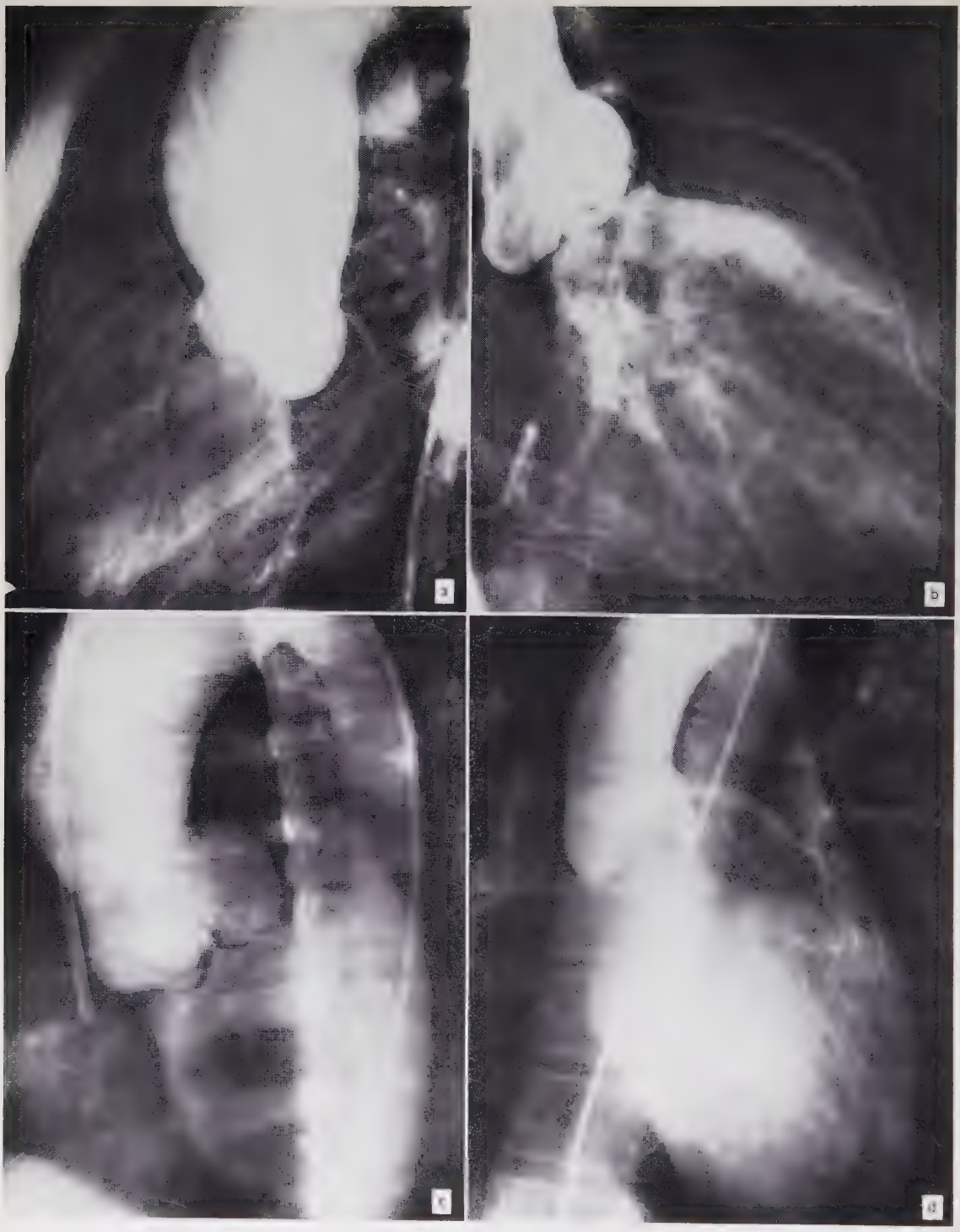

Fig. 17. Classification of aortic insufficiency. Thoracic aortography, diastole. *a*, Case 17, PSG 14 mm Hg. Grade 1 AI. *b*, Case 20, PSG 36 mm Hg. Grade 2 AI. *c*, Case 101, PSG 24 mm Hg. Grade 3 AI. *d*, Case 108, PSG 100 mm Hg. Grade 4 AI.

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